Wisconsin Card Sorting Test Scores and Relevant Clinical Factors in Schizophrenia: Multiple Logistic Regression Analysis

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Trish Groves, MD
Editor-in-chief
BMJ Open
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Dear Dr. Groves:

We hereby submit the enclosed full-length paper, "Wisconsin Card Sorting Test scores and relevant clinical factors in schizophrenia: multiple logistic regression analysis" by M. Banno *et al.* as an original contribution for consideration for publication in "*BMJ Open*". Neither the entire paper nor any of its contents have been accepted or submitted to any other journal.

Wisconsin Card Sorting Test (WCST) is a neurocognitive test and is one of the most frequently used executive function measures. WCST scores were related with social functioning in schizophrenic patients (*Psychiatry Research* 2011 187, 1-5). We believe that our work will be of interest to the readers of *BMJ Open* as our study is the first to focus on WCST factor scores in a Japanese population that looked into relationship between WCST factor score and clinical factors using a relatively large sample. We hope Table S1, S2, S3 and S4 will be published as Web only supplementary files.

None of the authors have financial or other relationships that would influence assessment of the data or that would constitute a conflict of interest. Each author contributed to the planning of the study and the writing of the manuscript, and each has read and approved all statements in it. We believe the manuscript presents important new findings and represents honest basic medical investigation and reporting. Please direct all correspondence to my address below.

Thank you in advance for your consideration of our paper.

Sincerely

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Wisconsin Card Sorting Test Scores and Relevant Clinical Factors in Schizophrenia: Multiple Logistic Regression Analysis

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ABSTRACT

Objectives: This study investigated what clinical factors affected Wisconsin Card Sorting Test (WCST) factor scores of schizophrenic patients to evaluate characteristics of the WCST based on correlation with clinical data.

Design: Cross-sectional study

Setting: Schizophrenic patients from three hospitals agreed to participate.

Participants: Recruitment for the participants occurred between July 2009 and August 2011. 131 Japanese schizophrenic patients (84 males and 47 females, 43.5±13.8 years (mean ± SD)) entered and completed the study. Participants were included in the study if they 1) met DSM-IV criteria for schizophrenia; 2) were physically healthy; and 3) had no mood disorders, substance abuse, neurodevelopmental disorders, epilepsy, or mental retardation. We examined their basic clinical factors (sex, age, education years, age of onset, duration of illness, chlorpromazine equivalent doses and the Positive and Negative Syndrome Scale [PANSS] scores).

Interventions: -

Primary and secondary outcome measures: All patients carried out the WCST Keio version and five indicators including Categories Achieved (CA), Perseverative Errors in Milner (PEM) and Nelson (PEN), Total Errors (TE), and Difficulties of Maintaining Set (DMS) were calculated.

Results: As the results of principal component analysis, we identified two factors (1 and 2). Factor 1 was mainly composed of CA, PEM, PEN, and TE. Factor 2

was mainly composed of DMS. We assessed relationship between these factor scores and clinical factors, using multiple logistic regression analysis. These results showed that the factor 1 score was affected by age, education years, and the PANSS negative scale. The factor 2 score was affected by duration of illness.

Conclusions: Age, education years, PANSS negative scale, and duration of illness affected WCST factor scores in schizophrenic patients. WCST factor scores may be useful to assess cognitive impairment in schizophrenic patients using WCST while avoiding problems from multiple comparisons.

Trial registration: -

ARTICLE SUMMARY

Article focus

- To investigate relationships between Wisconsin Card Sorting Test (WCST) factor scores and clinical factors in Japanese schizophrenic patients by multiple logistic regression analysis
- To show distributions of each WCST score for schizophrenic patients

Key messages

- Age, education years, Positive and Negative Syndrome Scale (PANSS) negative scale, and duration of illness affected two WCST factor scores.
- WCST factor scores calculated by principal component analysis may be useful for avoiding multiple comparison problems in investigating cognitive impairment in schizophrenic patients using WCST.

Strengths and limitations of this study

- We conducted principal component analysis and identified two WCST factors. Components of two WCST factors in this study were similar to previous studies.
- This is the first study to investigate relationships between WCST factor scores and clinical factors in schizophrenic patients.
- We identified a clinical factor (duration of illness) affecting WCST factor 2 score. This is a new finding.

INTRODUCTION

Cognitive impairment in patients with schizophrenia has been evaluated as an indicator of outcome regarding social functioning and quality of life.[1-2] It is reported that cognitive performance in patients with schizophrenia declines from prodrome to onset of schizophrenia (first episode). Moreover, it is reported that decline of cognitive performance exists before onset of schizophrenia. Many studies using brain structural and functional imaging suggest that progressive neurobiological changes in the brain relate to the cognitive impairment of schizophrenia. Therefore, some researchers regard cognitive impairment rather than positive and negative symptoms as the core pathology of schizophrenia.[3]

However, there are several problems when analyzing cognitive impairment in schizophrenia. First, positive and negative syndromes modify cognitive performance. Second, intelligence level, pattern of intelligence, and educational level at present and before onset of schizophrenia could affect cognitive impairment in patients with schizophrenia. In brief, many factors have the potential to affect cognitive impairment in schizophrenic patients. It is necessary to clarify the relationship between cognitive performance in schizophrenic patients and clinical factors in order to investigate what factors affect cognitive impairment in patients with schizophrenia.

Many neurocognitive tests have been used in order to evaluate cognitive performance in schizophrenia. The Wisconsin Card Sorting Test (WCST) is a neurocognitive test using cards and is one of the most frequently used executive function measures.[4] A functional brain imaging study showed widespread

activation across frontal and non-frontal brain regions during WCST performance.[5] Therefore, we investigated the relationship between WCST scores and clinical factors in this study. It has been reported that each WCST score was related with social functioning in schizophrenic patients.[6-8]

Recent reports suggest that WCST performance may decline from prodrome to onset of schizophrenia during progress of schizophrenia. A steady (nonsignificant) progression of impairment on WCST Perseverative Errors (PE) was demonstrated from basic symptom at-risk (BS), ultra high-risk (UHR), and first-episode (FE) groups (BS: z=–0.74; UHR: z=–0.88; FE: z=–0.97).[9] However, negative and depressive symptoms may modify WCST performance in schizophrenic patients,[10-11] and many other factors (for example, premorbid IQ) may modify WCST scores.

Factor structures of WCST in schizophrenic patients have been investigated using principal component analysis and factor analysis of WCST scores.[12-14] Differences in cognitive performance of WCST scores (Categories Achieved (CA), PE) and Wechsler Adult Intelligence Scale (WAIS) IQ were shown between schizophrenic patients and healthy controls (Cohens' d=0.91, 0.53 and 1.23) in one meta-analysis, but age, education years, and other clinical factors were not matched in the statistical analysis.[15] In other previous studies, age and education years affected CA and PE scores,[16] and Wechsler Adult Intelligence Scale-Revised (WAIS-R) Full Scale IQ (FSIQ), Verbal IQ (VIQ), and Performance IQ (PIQ) showed significant correlations (P<0.001) with CA and Total Errors (TE) scores in healthy controls.[17] Age affected PE scores but education years did not affect either CA or PE scores

[15]; age of onset affected PE scores [18] and the Positive and Negative Syndrome Scale (PANSS) negative scale affected CA score in schizophrenic patients.[10] These findings indicate that it is important to consider all clinical factors to clarify which affect WCST scores in schizophrenic patients.

WAIS FSIQ showed significant correlation (P<0.05) with CA, Perseverative Errors in Milner (PEM), and Nelson (PEN) and TE scores, item 3 and item 16 in Brief Psychiatric Rating Scale (BPRS) showed significant correlation (P<0.05) with CA, PEN and TE scores and affective flattening & blunting and avolition-apathy in Scale for the Assessment of Negative Symptoms (SANS) showed significant correlation (P<0.05) with CA, PEM, PEN, TE and Difficulties of Maintaining Set (DMS) scores of Wisconsin Card Sorting Test Keio version (KWCST) in Japanese schizophrenic patients (n=33).[19] However, there is no study that investigates other clinical factors (except IQ and negative symptoms) affecting KWCST scores. Therefore, we investigated clinical factors affecting scores of KWCST [20] (Japanese computerized version [21]) in Japanese schizophrenic patients.

METHODS AND PROCEDURES

Participants

The study included 131 unrelated Japanese schizophrenic patients (age 43.5±13.8 (mean ± SD), 84 males and 47 females) from three hospitals. Recruitment for the participants occurred between July 2009 and August 2011.

Profiles of all the patients are shown in Table 1.

This study protocol was approved by Nagoya University Graduate School of Medicine and Nagoya University Hospital Ethics Review Committee, and written informed consent was obtained from each participant. Participants were included in the study if they 1) met DSM-IV criteria for schizophrenia; 2) were physically healthy; and 3) had no mood disorders, substance abuse, neurodevelopmental disorders, epilepsy, or mental retardation. Consensus diagnoses were made by at least two experienced psychiatrists according to DSM-IV criteria on the basis of unstructured interviews with schizophrenic patients and families and review of medical records. Less than 5% of participants were excluded due to a lack of consensus.. All subjects were unrelated to each other, living in the central area of the mainland of Japan, and self-identified as Japanese. A general characterization and psychiatric assessment of the subjects is available elsewhere.[22-24]

Measurement Settings

WCST mainly assesses executive function including cognitive flexibility in response to feedback.[25] KWCST is the Japanese version of WCST modified by Kashima.[20] KWCST consists of a card version and a computerized version, both of which have been used in order to investigate cognitive performance in schizophrenic patients.[26-27] In KWCST, there are two levels of instruction.[28] The subject is told that, at the first level, this is a test of classification based on any of the three categories of color, shape, or number, and that, at the second level, the tester's categories change when the subject continues to get correct

answers at fixed times. We selected indicators (CA, PEM, PEN, TE and DMS) of KWCST in this analysis, given that these indicators were investigated in previous studies.[26-27] The computerized version uses instruction through letters on the monitor and they synthetic sound of the computer in order to prevent potential bias derived from confrontation test. The computerized test can investigate CA, PEM, PEN, TE and DMS scores. The computerized program investigates these indicators at the second level only if the CA score at the first level is equal or less than 3. We got data for the following five indicators [27, 29] at the first and second levels in this study.

(1) CA: the number of categories for which six consecutive correct responses are achieved (maximum CA is 8).

(2) PEM: the number of incorrect responses in the same category as the immediately preceding correct response after the tester's categories change (maximum PEM is 47).

(3) PEN: the number of incorrect responses in the same category as the immediately preceding incorrect response (maximum PEN is 47).

(4) TE: the total number of incorrect responses (maximum TE is 48).

(5) DMS: the number of times an incorrect response occurs after 2 to 5 consecutive correct responses (maximum DMS is 16).

We analyzed KWCST (Japanese computerized version [21]) (Shimane University, Shimane, Japan) scores of the schizophrenic patients at the first level.

Clinical factors

We investigated sex, age, education years, age of onset, duration of illness, chlorpromazine equivalent doses, and PANSS scores as clinical factors. Sex was categorized in terms of biology and was self-reported by the schizophrenic patients. Age was the schizophrenic patients' age on the day we evaluated KWCST scores. Education years were calculated from elementary school entrance to the graduation or dropout of the last institution of higher education, which consisted of junior high school, senior high school, vocational school, junior college, university and graduate school. Age of onset was the age at onset of schizophrenia in each patient and was based on review of medical records. Duration of illness was defined from age of onset to age at the time of study. Chlorpromazine (CPZ) equivalent doses were the identified dose ratios of each antipsychotic in relation to 100 mg of chlorpromazine.[30] CPZ equivalent doses in this study were calculated based on the method by Inagaki and Inada.[31-32] PANSS is a standardized scale in order to evaluate positive and negative symptoms of schizophrenia and was used to evaluate severity of schizophrenia in the patients.[33]

Statistical analysis

Clinical profiles of the schizophrenic patients are shown in Table 1. We investigated correlations of the five indicators of WCST (CA, PEM, PEN, TE and DMS) in schizophrenic patients by Spearman's Rank Correlation Test.

Principal component analysis

WCST factors were identified by principal component analysis of the five

indicators without rotation. Factors were retained using the eigenvalue >1 criterion.

Main analysis

In the main analysis, we investigated what clinical factors affected WCST factor scores in multiple logistic regression analysis. The dependent variables were WCST factor scores and independent variables were the following candidate clinical factors: sex, age, education years, age of onset, duration of illness, CPZ equivalent doses, and PANSS (positive, negative and general psychopathology scale) scores. We made a dummy conversion variable (1 or 0) for sex. We converted factor scores into categorical variables (1 or 0), using cutoff values that were median values of the factor scores.

In our multiple logistic regression analysis, we did additional two tests. First, we did an omnibus test of model coefficients versus a model with intercept only. This test detects whether a model is significant (P<0.05) or not; this is a test of the null hypothesis that adding any variables to the model has not significantly increased our ability to predict the dependent variable. A model is useless if the P-value in omnibus test was >0.05. Second, we did a Hosmer and Lemeshow goodness of fit test, which shows how well the model fits the data with P>0.05 indicating good fit; this is a test of the null hypothesis that there is a linear relationship between the predictor variables and the log odds of the criterion variable. The hit rate in multiple logistic regression analysis is a measure how well a model predicts the dependent variable.

Sub-analysis

In the sub-analysis, we also investigated what clinical factors affected the five indicators of WCST in the multiple logistic regression analysis. In this analysis, the dependent variables were the five indicators of WCST and independent variables were the candidate clinical factors. We compared the results of the multiple logistic regression analysis with the results of previous studies.[10, 15, 18]

Software

IBM SPSS statistical software (IBM Japan, Tokyo, Japan), version 19 was used for analyses. The significance level was set at P=0.05 using a two-tailed t-test.

RESULTS

Distributions of the WCST (CA, PEM, PEN, TE and DMS) scores in schizophrenic patients are shown in Figure 1. The numbers of schizophrenic patients in the following analyses were CA n=131, PEM n=122, PEN n=131, TE n=115 and DMS n=131 because of missing values in the data.

Spearman's rank correlation coefficients between five indicators of WCST are shown in Table 2. Although no strong correlation (>0.8) was observed in any of these clinical factors, the Spearman's correlation between PANSS negative scale and PANSS general psychopathology scale was high (0.74).

Principal component analysis

Two factors (1 and 2) were identified in principal component analysis of the five indicators of WCST. Factor 1 mainly consisted of CA, PEM, PEN, and TE, and accounted for 65.6% of the total variance. Factor 2 mainly consisted of DMS and accounted for 23.2% of the total variance (Table 3 and Figure 2). We converted the factor 1 and factor 2 scores into categorical variables (1 or 0) using cutoff values. The cutoff values were the median values (factor 1: -0.299; factor 2: 0.080). We used these categorical variables as dependent variables in multiple logistic regression analysis.

Main analysis

Age, education years, and PANSS negative scale significantly affected factor 1 scores, and the duration of illness significantly affected factor 2 scores in schizophrenic patients (Table 4). The details of the results from the multiple logistic regression analyses are shown in Table S1 (Web only files). *P*-values in an omnibus test of model coefficients versus a model with intercept only were statistically significant ($P<0.05$) for all the models in WCST factor scores. In the Hosmer and Lemeshow goodness of fit test, all the models fit the data adequately with $P>0.05$. Factor 1 score may be predicted by this model precisely considering hit rate (0.77).

Sub-analysis

In the sub-analyses, age, education years, and PANSS negative scale significantly affected CA score, age and education years significantly affected PEM, PEN, and TE scores, and age significantly affected DMS score in

schizophrenic patients. The details of these results are shown in Table S2 and Table S3 (Web only files); Table S3 includes the results of previous studies. *P*-values in omnibus test of model coefficients versus a model with intercept only were statistically significant ($P<0.05$) for all the models for each WCST score, and all the models did fit the data adequately in the Hosmer and Lemeshow goodness of fit test.

DISCUSSION

This study is the first to investigate the relationships between WCST factor scores and clinical factors in Japanese schizophrenic patients by multiple logistic regression analysis. We showed the distribution of each WCST score (Figure 1). We conducted principal component analysis and identified two factors. Components of two factors were similar to previous studies.[12-14] Thus, we could reduce the number of WCST outcomes from five indicators to two factors (Table 3). This might be useful for avoiding multiple comparison problems in assessing cognitive function in schizophrenia. Using these two WCST factors, we analyzed the relationship between these two factors and clinical factors with multiple logistic regression analysis. We found that age, education years, PANSS negative scale, and duration of illness affected the two WCST factor scores.

Principal component analysis

Our study showed that factor 1 mainly consisted of CA, PEM, PEN, and TE and factor 2 mainly consisted of DMS. In the previous studies with principal

component analysis and factor analysis of WCST scores in schizophrenic patients, Categories Complete (CC) (indicator examining numbers of categories achieved in the same way as CA), PE (indicator examining perseveration in the same way as PEM and PEN) and TE mainly constituted one factor. Failure to Maintain Set (FMS) (indicator examining difficulty of maintaining set in the same way as DMS) mainly constituted another factor.[12-14] Our results resembled the results of the principal component analysis and factor analysis of WCST in these previous studies.[12-14]

Factor 1, which included representative indicators (CC, PE, etc.), was named as 'general executive functioning' in a previous study.[14] Therefore, factor 1 in our study also may represent general executive functioning. In our study, factor 1 scores showed a high contribution ratio of the total variance (65.6%) in principal component analysis of WCST scores in schizophrenic patients. WCST factor scores calculated by principal component analysis may be useful for avoid multiple comparison problem to investigate cognitive impairment in schizophrenic patients using WCST.

Factor 1 and factor 2 in our study resembled those in previous studies.[12-14] Therefore, the KWCST measures cognitive function similarly to the traditional WCST, although different versions of WCST exist, for example, the different card numbers and computer based or not.

Main analysis

We identified clinical factors (age, education years and PANSS negative scale) affecting WCST factor 1 score. We also identified a clinical factor

(duration of illness) affecting WCST factor 2 score. This is an important new finding. Comparing the three main previous studies [10, 15, 18] with the current study, we summarized the shared findings and different findings, shown in Table 4.

In shared findings, age was related to PE score in a previous study [15] and age was related to the factor 1 score (mainly consisting of CA, PEM, PEN, and TE scores) in our study. Second, PANSS negative scale was related to CA score in a previous study [10] and PANSS negative scale was related to factor 1 score (CA, PEM, PEN and TE scores) in our study. Therefore, the shared findings were that age and PANSS negative scale were related to WCST scores.

On the other hand, our study showed different findings from previous studies (Table 4).[10, 15, 18] First, education years were not related to CA and PE scores in the previous study [15], but were related to the factor 1 score in our study. Second, age of onset was related to the PE score in a previous study [18] but was not related to factor 1 score in our study. Differences in the results between previous studies and our study [10, 15, 18] may be explained by differences of ethnicity, distributions of age and education years, types of statistical analysis used, and the version of WCST. These differences suggest that future studies about WCST should be conducted with attention to these conditions.

Sub-analysis

Compared with the main analysis, clinical information related to the main components (CA, PEM, PEN and TE) of factor 1 and clinical information related

to factor 1 score by principal component analysis were similar (Table S4 (Web only files)). Clinical information related to the DMS score was different from clinical information related to factor 2 score; however, both relationships were weak (Table S4 (Web only files)). This may be derived from the finding that factor 2 included not only the DMS, but also CA, PEM, PEN, and TE.

Limitations

There are several limitations in this study. First, other clinical factors that were not investigated in the current study could affect WCST scores. Candidates of such clinical factors are IQ,[17] participants' dominant arm, experience with using a computer, doses of drugs affecting cognitive performance (anticholinergics, benzodiazepines, etc), sleep,[34] eating, and risk factors of arteriosclerosis (BMI, blood pressure, etc).[35] It may be useful to include these factors in future studies. Second, WCST indicators (CA, PEM, PEN, TE and DMS scores) in our study did not cover all the WCST indicators; we selected the major five indicators. We might find other factors by principal component analysis or new relationships between new WCST factors and clinical factors if we included other clinical indicators.

Conclusion

This study is the first study that investigated clinical factors affecting WCST factor scores calculated by principal component analysis in schizophrenic patients. The study was conducted in a relatively large Japanese population. We

showed distributions of measured five WCST indicators in schizophrenic patients and confirmed two WCST factors by principal component analysis. Age, education years, PANSS negative scale, and duration of illness affected WCST scores in schizophrenic patients.

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FOOTNOTES

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Core Research for Evolutional Science and Technology. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests

None

Ethics approval

This study was approved under the guidelines for epidemiological studies by the Nagoya University Graduate School of Medicine and Nagoya University Hospital Ethics Review Committee and was conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from each subject before the start of the study.

Contributors

MB, TKo and NO conceived and designed the experiments. MB, TKo, TKi, KK and YA performed the experiments. MB, TKo, BA, TO, NK, TI and NO analyzed the data. MB, TKo and YA contributed reagents/materials/analysis tools. MB, TKo, TO, BA and NO wrote the paper.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

No additional data are available.

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FIGURE LEGENDS

Figure 1. Distributions of WCST scores in schizophrenic patients (*n*=131)

None of the distributions were normal distributions.

Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set

[a]. Standard deviation

[b]. % of cases

Figure 2. Component plot in principal component analysis of WCST scores in schizophrenic patients (*n*=131)

Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set

Table 1. Profiles of schizophrenic patients

Table 2. Correlation coefficients for WCST scores in schizophrenic patients

Table 3. Factor loadings in principal component analysis in schizophrenic patients (*n*=131)

Table 4. Clinical factors for WCST scores of schizophrenic patients in the

current study (main analysis) and for previous studies

APPENDICES

Table S1 (Web only files). Multiple logistic regression analysis of WCST factor scores in patients with schizophrenia (*n*=131)

Table S2 (Web only files). Multiple logistic regression analysis of WCST scores in patients with schizophrenia (*n*=131)

Table S3 (Web only files). Clinical factors for WCST scores of schizophrenic patients in this study (sub-analysis) and previous studies

Table S4 (Web only files). Clinical factors for WCST scores of schizophrenic patients in this study (main analysis and sub-analysis)

Table 1. Profiles of schizophrenic patients

			Schizophrenic patients (n=131)	
Sex			Male	Female
			84	47
			Average	(SD[a])
Age (y)			43.5	(13.8)
Education years (y)			12.4	(2.4)
Age of onset (y)			26.3	(10.0)
Duration of illness (y)			17.0	(12.8)
Chlorpromazine equivalent doses (mg)			618.4	(391.1)
PANSS scale		Positive (7-49)	16.5	(5.3)
		Negative (7-49)	19.3	(5.6)
		General (16-112)	36.6	(9.4)
		Total (30-210)	72.4	(18.1)
Clinical diagnosis		Paranoid type	48	
		Disorganized type	6	
		Residual type	67	
		Catatonic type	1	
		Undifferentiated type	1	
		Unknown	8	
Antipsychotics	Monotherapy	Risperidone	54	
		Olanzapine	18	
		Aripiprazole	17	
		other atypical	5	
		typical	1	
	Polytherapy		36	

[a]. Standard deviation

Table 2. Correlation coefficients for WCST scores in schizophrenic patients

		Schizophrenic patients (*n*=131)				
		CA	PEM	PEN	TE	DMS
correlation coefficient[a]	CA	-	-	-	-	-
	PEM	-0.70**	-	-	-	-
	PEN	-0.79**	0.73**	-	-	-
	TE	-0.88**	0.71**	0.89**	-	-
	DMS	-0.58**	0.30*	0.28*	0.30*	-

*: $P<0.01$, **: $P<0.001$

Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set

[a]. Spearman's rank correlation coefficient

Table 3. Factor loadings in principal component analysis in schizophrenic patients (*n*=131)

		factor 1	factor 2
WCST score	CA	-0.89	0.36
	PEM	0.84	0.27
	PEN	0.92	0.27
	TE	0.93	0.13
	DMS	0.29	-0.93
Variance (%) explained by each factor		65.6	23.2
Cumulative explained variance (%)		65.6	88.9

Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set

Factor analysis was based on principal component method without rotation.

Two factors were retained using the eigenvalue >1 criterion.

Table 4. Clinical factors for WCST scores of schizophrenic patients in the current study (main analysis) and for previous studies

		Schizophrenic patients (n=131) Main analysis		Previous studies		
		Factor 1 score	Factor 2 score	CA[a]	PE[a]	TE[a]
Sex				n/a	n/a	n/a
Age		***		n.s.	○[b]	n/a
Education years		**		n.s.	n.s.	n/a
Age of onset				n/a	○[c]	n/a
Duration of illness			*	n/a	n/a	n/a
Chlorpromazine equivalent doses				n/a	n/a	n/a
PANSS score	positive (7-49)			n/a	n/a	n/a
	negative (7-49)	*		○[d]	n/a	n/a
	general (16-112)			n/a	n/a	n/a
hit rate		0.77	0.58	n/a	n/a	n/a

*: P<0.05, **: P<0.01, ***: P<0.001

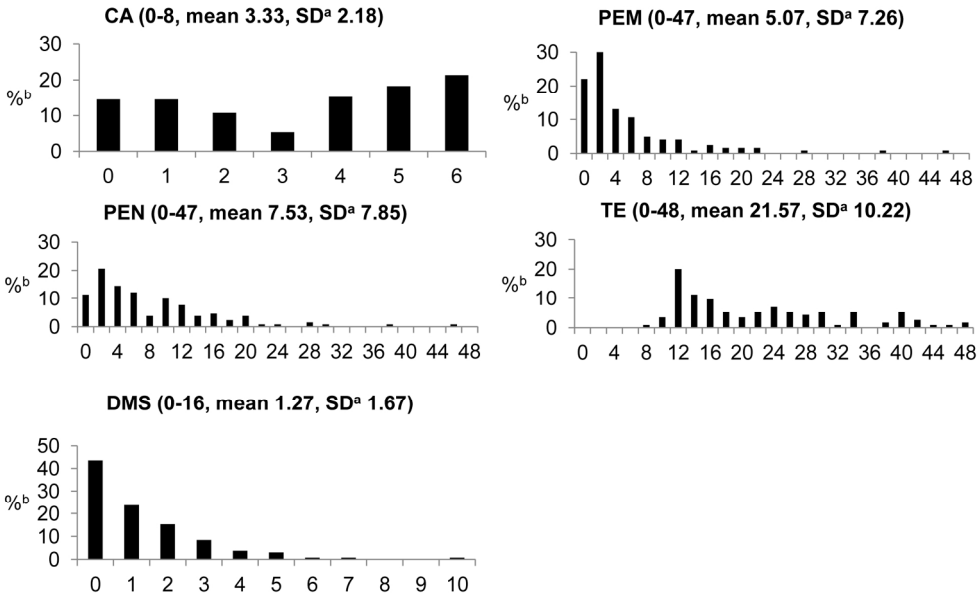
Abbreviations: CA, Categories Achieved; PE, Perseverative errors; TE, Total Errors; n/a, data not available; n.s., not significant

[a]. CA, PE and TE were included in factor 1 in a previous study.

[b]. Reference 15

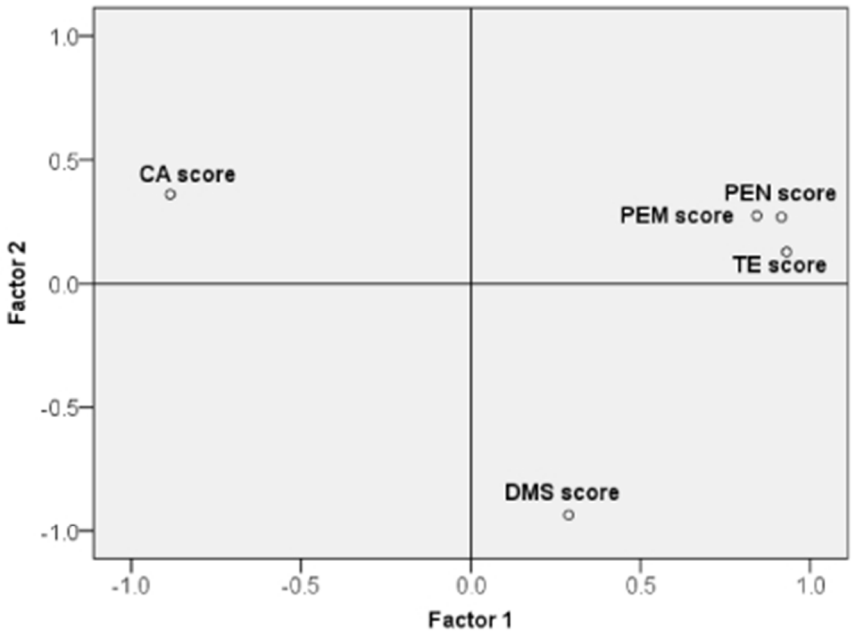
[c]. Reference 18

[d]. Reference 10



None of the distribution was normal distribution.
Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set
[a]. Standard deviation
[b]. % of cases

169x104mm (300 x 300 DPI)



Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set
36x27mm (300 x 300 DPI)

Table S1. Multiple logistic regression analysis of WCST factor scores in patients with schizophrenia (*n*=131)

Forward-backward stepwize selection, Setting: P_{in}=0.05, P_{out}=0.1								
		Factor 1 score				Factor 2 score			
		B[a]	Exp(B)[b]	95% CI[c]	*P*-value	B[a]	Exp(B)[b]	95% CI[c]	*P*-value
Sex (Male 1, Female 0)		-	-	-	-	-	-	-	-
Age (y)		0.06	1.06	1.03-1.10	**<0.001**	-	-	-	-
Education years (y)		-0.39	0.68	0.54-0.85	**0.001**	-	-	-	-
Age of onset (y)		-	-	-	-	-	-	-	-
Duration of illness (y)		-	-	-	-	-0.03	0.97	0.94-1.00	**0.03**
CPZeq (mg/day)		-	-	-	-	-	-	-	-
PANSS score	Positive (7-49)	-	-	-	-	-	-	-	-
	Negative (7-49)	0.11	1.12	1.02-1.22	**0.01**	-	-	-	-
	General (16-112)	-	-	-	-	-	-	-	-
Intercept		-0.03	0.97	-	0.98	0.55	1.73	-	0.08
omnibus test		***P*<0.001**				**0.02**			
Hosmer and Lemeshow test		0.12				0.85			
hit rate		0.77				0.58			

Abbreviations: CPZeq, Chlorpromazine equivalent doses

[a]. Regression coefficient

[b]. This is the exponentiation of the B coefficient, which is an odds ratio.

[c]. Confidence interval of Exp(B)

Cutoff values were factor 1: -0.299, factor 2: 0.080.

0 and 1 are dummy variables in respect to subjects' sex.

Considering omnibus test *P*-values, these models are significant (*P*<0.05).

Considering Hosmer and Lemeshow test *P*-values (*P*>0.05), factor 1 score and factor 2 score may be predicted by this model.

Table S2. Multiple logistic regression analysis of WCST scores in patients with schizophrenia (*n*=131)

		Forward-backward stepwize selection, Setting: P_{in}=0.05, P_{out}=0.1																			
		CA				PEM				PEN				TE				DMS			
		B[a]	Exp(B)[b]	95% CI[c]	*P* -value	B[a]	Exp(B)[b]	95% CI[c]	*P* -value	B[a]	Exp(B)[b]	95% CI[c]	*P* -value	B[a]	Exp(B)[b]	95% CI[c]	*P* -value	B[a]	Exp(B)[b]	95% CI[c]	*P* -value
Sex (Male 1, Female 0)		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Age (y)		-0.06	0.94	0.92-0.97	**<0.001**	0.03	1.03	1.00-1.06	**0.04**	0.05	1.05	1.02-1.08	**0.001**	0.06	1.06	1.03-1.10	**<0.001**	0.03	1.03	1.01-1.06	**0.02**
Education years (y)		0.31	1.36	1.13-1.64	**0.001**	-0.33	0.72	0.59-0.87	**0.001**	-0.19	0.83	0.70-0.97	**0.02**	-0.35	0.70	0.57-0.87	**0.001**	-	-	-	-
Age of onset (y)		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Duration of illness (y)		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CPZeq (mg/day)		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PANSS score	Positive (7-49)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Negative (7-49)	-0.08	0.92	0.85-0.99	**0.03**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	General (16-112)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Intercept		0.52	1.68	-	0.72	3.21	24.70	-	**0.02**	0.37	1.45	-	0.76	1.76	5.79	-	0.22	-1.12	0.33	-	0.07
omnibus test		***P* <0.001**				***P* <0.001**				***P* <0.001**				***P* <0.001**				**0.02**			
Hosmer and Lemeshow test		0.44				0.76				0.56				0.56				0.88			
hit rate		0.69				0.66				0.62				0.71				0.60			

Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set; CPZeq, Chlorpromazine equivalent doses

[a]. Regression coefficient

[b]. This is the exponentiation of the B coefficient, which is an odds ratio.

[c]. Confidence interval of Exp(B)

Cutoff values were CA: 4, PEM: 2, PEN: 5, TE: 18, DMS: 1.

0 and 1 are dummy variables in respect to subjects' sex.

Considering omnibus test *P*-values, these models are significant (*P*<0.05).

Considering Hosmer and Lemeshow test *P*-values (0.05<*P*), CA, PEN, PEM, TE and DMS scores may be predicted by this model.

Table S3. Clinical factors for WCST scores of schizophrenic patients in this study (sub-analysis) and previous studies

		Schizophrenic patients (n=131) Sub-analysis					Previous studies		
		CA	PEM	PEN	TE	DMS	CA	PE	TE
Sex							n/a	n/a	n/a
Age		***	*	**	***	*	n.s.	○[a]	n/a
Education years		**	**	*	**		n.s.	n.s.	n/a
Age of onset							n/a	○[b]	n/a
Duration of illness							n/a	n/a	n/a
Chlorpromazine equivalent doses							n/a	n/a	n/a
PANSS score	positive (7-49)						n/a	n/a	n/a
	negative (7-49)	*					○[c]	n/a	n/a
	general (16-112)						n/a	n/a	n/a
hit rate		0.69	0.66	0.62	0.71	0.60	n/a	n/a	n/a

*: P<0.05, **: P<0.01, ***: P<0.001

Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set; PE, Perseverative errors; n/a, data not available; n.s., not significant

[a]. Reference 15

[b]. Reference 18

[c]. Reference 10

Table S4. Clinical factors for WCST scores of schizophrenic patients in this study (main analysis and sub-analysis)

	Schizophrenic patients (n=131)						
	Main analysis		Sub-analysis				
	Factor 1 score	Factor 2 score	CA[a]	PEM[a]	PEN[a]	TE[a]	DMS[b]
Sex							
Age	***		***	*	**	***	*
Education years	**		**	**	*	**	
Age of onset							
Duration of illness		*					
Chlorpromazine equivalent doses							
PANSS score positive (7-49)							
PANSS score negative (7-49)	*		*				
PANSS score general (16-112)							
hit rate	0.77	0.58	0.69	0.66	0.62	0.71	0.60

*: P<0.05, **: P<0.01, ***: P<0.001

Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set

[a]. CA, PEM, PEN and TE were included in factor 1 in this study.

[b]. DMS was included in factor 2 in this study.

BMJ open

Wisconsin Card Sorting Test Scores and Clinical and Socio-demographic Correlates in Schizophrenia: Multiple Logistic Regression Analysis

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Secondary Subject Heading:	Mental health
Keywords:	Schizophrenia & psychotic disorders < PSYCHIATRY, MENTAL HEALTH, Adult psychiatry < PSYCHIATRY

September 8th, 2012

Trish Groves, MD
Editor-in-chief
BMJ Open
BMA House, Tavistock Square
London WC1H 9JR
UK

Dear Dr. Groves:

We hereby submit the revised full-length paper, "Wisconsin Card Sorting Test Scores and Clinical and Socio-demographic Correlates in Schizophrenia: Multiple Logistic Regression Analysis" by M. Banno *et al.* as an original contribution for consideration for publication in "*BMJ Open*". Neither the entire paper nor any of its contents have been accepted or submitted to any other journal.

The Wisconsin Card Sorting Test (WCST) is a neurocognitive test and is one of the most frequently used measures of executive function. WCST scores have been related to social functioning in schizophrenic patients (*Psychiatry Research* 2011 187, 1-5). We believe that our work will be of interest to the readers of *BMJ Open* as our study is the first to focus on WCST factor scores in a Japanese population that looked into relationship between WCST factor score and clinical factors using a relatively large sample. We hope Tables S1, S2, S3, and S4 and Information S1 and S2 will be published as Web only supplementary files.

None of the authors have financial or other relationships that would influence assessment of the data or that would constitute a conflict of interest. Each author contributed to the planning of the study and the writing of the manuscript, and each has read and approved all statements in it. We believe the manuscript presents important new findings and represents honest basic medical investigation and reporting. Please direct all correspondence to my address below.

Thank you in advance for your consideration of our paper.

Sincerely

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Responses to Reviewer #1

We are grateful to reviewer #1 for the critical comments and useful suggestions that have helped us to considerably improve our manuscript. As indicated in the responses that follow, we have taken all of these comments and suggestions into account in the revised version of our manuscript.

1. In general, this manuscript still needs an English proof reading in order to correct some grammatical errors and help readers to understand authors' messages better.

Thank you very much for your comments. We took advantage of professional English proofreading to correct grammatical errors and help readers to understand our messages better before we submitted the original manuscript and revised manuscript.

2. Abstract

A. Please revise the term "schizophrenic patients" into "patients with schizophrenia". Results, page 4, line 6-8, "We assessed relationship between these factor scores and clinical factors, using multiple logistic regression analysis." should be moved into the previous part, Primary and secondary outcome measures.

Thank you very much for your comments. We revised the term "schizophrenic patients" as "patients with schizophrenia" in manuscript, figures and tables.

We moved "From the principal component analysis, we identified two factors (1 and 2). We assessed the relationship between these factor scores and clinical and socio-demographic factors, using multiple logistic regression analysis." into Primary and secondary outcome measures.

3. Introduction

A. It should focus more on the key issues that authors wish to investigate and avoid unnecessary information in order to clearly show the main aims of this study, for example, IQ related information may not be necessary.

Thank you very much for your comment. According to the reviewer's suggestion,

we have shortened the introduction section by deleting some of the IQ related information.

B. The 1st paragraph (Page 6, Line 12-19, 19-25) and 2nd paragraph shall have references added. The 2nd paragraph, page 6, line 34, please clarify the meaning of "pattern of intelligence".

Thank you very much for your comment. We added references to the 1st paragraph (Page 6, Line 4-8, 8-10) and 2nd paragraph.

We revised Page 6, Line 8-10 and Line 15-17 considering the contents of the references.

Revised manuscript (Page 6, Line 8-10): Introduction

"Many studies using brain imaging suggest that neurobiological changes in the brain are related to the cognitive impairment in schizophrenia."

Revised manuscript (Page 6, Line 15-17): Introduction

"Second, intelligence level, intelligence profile (verbal IQ and performance IQ), and educational level could affect cognitive impairment in patients with schizophrenia."

Page 6, Line 15, "pattern of intelligence" meant intelligence profile (verbal IQ and performance IQ). Therefore, we revised the manuscript as follows.

Revised manuscript (Page 6, Line 15-16): Introduction

"intelligence profile (verbal IQ and performance IQ)"

C. Page 6, line 56 and page 7, line 6-10, this paragraph sounded odd. Page 7, line 27-29, a reference may be necessary to support this statement.

Thank you very much for your comment. We removed the unnecessary sentence "Therefore, we investigated the relationship between WCST scores and clinical factors in this study." from the paragraph. We also added references to Page 7, Line 11-12.

4. Methods and procedures

A. The recruitment of participants, authors shall mention from which department in 3 hospitals the recruitment took place, the outpatient department or the acute or/chronic ward? Since the relation between the severity of psychotic symptoms and WCST was investigated later in this study. Is there any concordant medication used by patients in spite of antipsychotics, such as anxiolytics, BZD etc. (Table 1, polytherapy)? The WCST assessment procedure, who performed the assessment?

Thank you very much for your comments. The recruitment took place from both the outpatient department and the acute / chronic wards in three hospitals. 51 outpatients (15 acute phase patients and 36 chronic phase patients) and 55 inpatients (37 acute phase patients and 18 chronic phase patients) were recruited. 25 patients were unspecified (outpatients or inpatients: 20 acute phase patients and 5 chronic phase patients). We did not select outpatients / inpatients as an independent variable in main and sub-analysis, because we could not obtain the information about outpatients / inpatients in 19% of the subjects. We revised manuscript as follows.

Revised manuscript (Page 8, Line 24-Page 9, Line 4): Methods and procedures

"The recruitment took place from both the outpatient department and the acute / chronic wards in three hospitals. 51 outpatients (15 acute phase patients and 36 chronic phase patients) and 55 inpatients (37 acute phase patients and 18 chronic phase patients) were recruited. 25 patients were unspecified (outpatients or inpatients: 20 acute phase patients and 5 chronic phase patients)."

104 patients (78%) were receiving concomitant medications including benzodiazepines, barbiturates, anticholinergics, mood stabilizers, and antidepressants. Polytherapy in Table 1 meant therapy using two or more antipsychotics. We revised the manuscript as follows.

Revised manuscript (Page 9, Line 6-8): Methods and procedures

"104 patients (78%) were receiving concomitant medications, which could include benzodiazepines, barbiturates, anticholinergics, mood stabilizers, and antidepressants."

Psychiatrists in three hospitals performed the assessment. We revised manuscript as follows.

Revised manuscript (Page 11, Line 4-5): Methods and procedures

"Psychiatrists in three hospitals performed the KWCST assessment.**"**

B. Page8, line 56, "Recruitment for the participants occurred between July 2009 and August 2011. "would be better to revised into " Participants were recruited from July 2009 to August 2011."

Thank you very much for your comments. We revised Page 9, Line 4-5 according to the reviewer's suggestion.

Revised manuscript (Page 9, Line 4-5): Methods and procedures

"Participants were recruited from July 2009 to August 2011."

C. Page 9, line 14 "included" shall be "recruited"; line 30, why did authors mention " ….and self-identified as Japanese." about the subjects? Please clarify this statement.

Thank you very much for your comments. We revised Page 9, Line 12 from "included" to "recruited".

"and self-identified as Japanese" meant we recruited Japanese patients. We removed this part in order to help readers to understand better.

D. Page 11, line 10-12, please clarify this statement: "Sex was categorized in terms of biology and was self-reported by the schizophrenic patients."

Thank you very much for your comments. "Sex was categorized in terms of biology and was self-reported by the schizophrenic patients." meant we determined the sex of participants according to their self-reports. We revised Page 11, Line 10 as follows.

Revised manuscript (Page 11, Line 10): Methods and procedures

"Sex was determined by patients' self-reports."

5. Statistical analysis

A. The rationale and methodology (i.e. Kaiser's criteria and unrotated solution) of applying principle component analysis as a mean of data reduction are appropriate. However, to dichotomize the continuous factor scores by using the median as a cutoff point for logistic regression may be unjustified yet. What were the scores of factors referred to? Furthermore, for logistic regression analysis, the authors converted factor scores into categorical variables by using the median as a cutoff point, is there any reference to support this method? No strong rationale (e.g. for moderator analysis, for risk factor analysis between case and non-case) could be found to use logistic regression in this study yet. A series of multiple linear regressions as the main analysis would be better suitable.

Thank you very much for your comments. The reason we adopted the multiple logistic regression was the distribution of dependent variables (WCST factor scores). To conduct multiple linear regression analysis, normality of dependent variables is needed. (Osborne JW, Waters E. Four Assumptions Of Multiple Regression That Researchers Should Always Test. Practical Assessment, Research, and Evaluation 2002;**8**:1-9.) About the distribution of dependent variables (WCST factor scores) in this study, *P*-values of two kinds of normality test (Kolmogorov-Smirnov test and Shapiro-Wilk test) were less than 0.001. We also tested normality of the logarithmic distribution of dependent variables (WCST factor scores), and the *P*-values of two kinds of normality test (Kolmogorov-Smirnov test and Shapiro-Wilk test) were less than 0.001. Multiple logistic regression can analyze variables in non-normality. (Peng CYJ, Lee KL, Ingersoll GM. An introduction to logistic regression analysis and reporting. J Educ Res 2002;**96**:3-14.)

We added a supplementary file, Information S1 (Web only file), to explain why we did not use multiple linear regression analysis.

We converted factor scores into categorical variables for multiple logistic regression analysis because dependent variables in multiple logistic regression analysis should be binary values. There were two reasons that we used the median as a cutoff point for the dependent variables (WCST factor scores) in the multiple logistic regression analysis. First, one previous psychiatric research study used the median as a cutoff point in dependent

variables of multiple logistic regression analysis. (Jackson CT, Fein D, Essock SM, Mueser KT. The effects of cognitive impairment and substance abuse on psychiatric hospitalizations. Community Ment Health J 2001;**37**:303-12.) Second, the most common approach was to take the sample median in dichotomizing continuous variables because there were no cutoff points of WCST factor scores in previous studies. (Altman DG, Royston P. The cost of dichotomising continuous variables. BMJ 2006;**332**:1080.)

We provided a supplementary file, Information S2 (Web only file) in order to explain the reason we used the median as a cutoff point for the dependent variables (WCST factor scores) in the multiple logistic regression analysis.

We also added a statement about the limitations of dichotomizing continuous variables (WCST factor scores).

Revised manuscript (Page 19, Line 21-24): Discussion

"Third, we dichotomized continuous variables (WCST factor scores) in the multiple logistic regression analysis. Therefore, careful interpretation of the results may be needed, considering the statistical weak points of dichotomizing continuous variables. (Altman DG, Royston P. The cost of dichotomising continuous variables. BMJ 2006;**332**:1080.)"

6. Results

A. The effect of duration of illness on one factor of WCST (i.e. factor 2 was influenced by DMS) is the novel finding of this study, table 4. However, another analysis (table S4) also showed that DMS is not significantly associated with the duration of illness. This discrepancy between the Main analysis and Sub-analysis should be explained carefully in order to conclude this novel finding.

Thank you very much for your comments. The effect of duration of illness on WCST factor 2 score (i.e. factor 2 was mainly influenced by DMS) is the novel finding in main analysis. However, DMS is not significantly associated with the duration of illness in sub-analysis (Table S4 (Web only file)). This discrepancy between the main analysis and sub-analysis may be derived from the difference between DMS and factor 2 (Factor 2 included not only the DMS, but also CA, PEM, PEN and TE). We added this discussion to our manuscript as follows.

Revised manuscript (Page 19, Line 1-6): Discussion

"The effect of duration of illness on WCST factor 2 score, which was mainly influenced by DMS, is the novel finding of the main analysis. However, DMS is not significantly associated with the duration of illness in the sub-analysis (Table S4 (Web only file)). This discrepancy between the main analysis and sub-analysis may be derived from the difference between DMS and factor 2 (Factor 2 included not only DMS, but also CA, PEM, PEN and TE)."

B. Table 1, the subtypes of schizophrenia and even the variety of antipsychotics could be deleted since they were not applied in the analyses.

Thank you very much for your comments. We deleted the subtypes of schizophrenia and the variety of antipsychotics in Table 1.

7. Discussion and Limitations

A. Page 17, the 2nd and 3rd paragraphs need to be revised in order to help readers to understand better.

Thank you very much for your comments. We revised these paragraphs, Table 4 and Table S3 in order to help readers to understand better.

Revised manuscript (Page 17, Line 22-Page 18, Line 7): Discussion

"The shared findings were that age and PANSS negative scale score were related to WCST scores (Table 4).[9 10 23]

Two findings differed from previous studies (Table 4).[9 10 23] First, we found a new relationship between education years and WCST scores. Second, we found no relationship between age of onset and WCST scores. Differences in the results between previous studies [9 10 23] and our study may be explained by differences of ethnicity, distribution of age and education years, types of statistical analysis used, and the version of WCST. These differences suggest that future studies about WCST should be conducted with attention to these conditions."

B. Sub-analysis, page 17, line 54 and page 18, 1st paragraph need to be revised in

order to help readers to understand better.

Thank you for pointing this out. We revised the manuscript as follows.

Revised manuscript (Page 18, Line 22-24): Discussion

"We found that factor 1 score and factor 1 score's main components (CA, PEM, PEN and TE) related to age and education years (Table S4 (Web only file))."

C. The Chlorpromazine equivalent doses did not affect the WCST and the different effects of PANSS (positive, negative) toward WCST should be mentioned and interpreted.

In the revised manuscript, we mentioned and interpret this result.

Revised manuscript (Page 15, Line 10-12): Results

"CPZ equivalent doses did not affect the WCST scores. PANSS positive scale score did not affect the WCST scores; whereas PANSS negative scale score did."

Revised manuscript (Page 18, Line 8-18): Discussion

"CPZ equivalent doses did not affect the WCST scores in this study. This result was in the same direction as one meta-analysis (n=4524) though recent studies had suggested the possibility of an effect.[31 39 40] Future studies will be necessary to clarify whether CPZ equivalent doses affect WCST scores under other conditions.

PANSS positive scale score did not affect the WCST scores but the PANSS negative scale score did. A recent meta-analysis (n=6519) suggested that negative symptoms related to cognitive performance in patients with schizophrenia whereas positive symptoms did not.[41] This suggests that the relationships between PANSS positive and negative scale scores and WCST scores in this study may be reasonable."

8. Conclusion

A. The significant interaction between the duration of illness and a factor of WCST could not be concluded yet and it needs further confirmation.

Thank you very much for your comments. We agree that this needs further confirmation in future studies because of the discrepancy between the results of main analysis and sub-analysis in this study. We revised the manuscript as follows.

Revised manuscript (Page 20, Line 10-13): Conclusion

"The interaction between the duration of illness and a factor of the WCST needs further confirmation in future studies because there was a discrepancy between the results of the main analysis and the sub-analysis in this study."

Responses to Reviewer #2

We would like to express our gratitude to the reviewer #2 for the critical comments and useful suggestions that have helped us to considerably improve our manuscript. As indicated in the responses that follow, we have taken all these comments and suggestions into account in the revised version of our manuscript.

1. The English language used in the manuscript is very poor and hard to follow, the title of the manuscript is not really reflecting what authors found. It's not only about clinical factors in schizophrenia but also sociodemographic factors and I would suggest to use ' clinical and socio demographic correlates in schizophrenia ' instead of ' factors '
It has been mentioned several times the word ' WCST characteristics ' though different subcategories measured by WCST are better described as ' WCST parameters or items '

Thank you very much for your comments. We took advantage of professional English proofreading to correct grammatical errors and help readers to understand our message better before we submitted the original manuscript and revised manuscript.

We changed the title of the manuscript following the reviewer's suggestion. The new title was "**Wisconsin Card Sorting Test Scores and Clinical and Socio-demographic Correlates in Schizophrenia: Multiple Logistic Regression Analysis**". We changed the term 'clinical factors' to 'clinical and socio-demographic factors' in the manuscript, figures and tables.

We changed the term ‘WCST characteristics’ to ‘WCST parameters or items’.

2. Though results are interesting, and to my knowledge it's the first time to correlate different demographic parameters to performance on WCST, which render such research work innovative. But authors did not provide an explanation of their own to findings, of particular interest the poor performance that was correlated to score on the negative subscale of the PANSS a finding that contradicts many authors supporting the idea that cognitive impairment is not correlated to negative or positive subscales of PANSS and should be considered a separate entity.

Thank you very much for your comments. We discussed and provided an explanation about the relationship between PANSS positive and negative scale scores and cognitive performance in patients with schizophrenia.

Revised manuscript (Page 18, Line 13-18): Discussion

“PANSS positive scale score did not affect the WCST scores but the PANSS negative scale score did. A recent meta-analysis (n=6519) suggested that negative symptoms related to cognitive performance in patients with schizophrenia whereas positive symptoms did not.[41] This suggests that the relationships between PANSS positive and negative scale scores and WCST scores in this study may be reasonable.”

3. The phrase in conclusion section ' WCST factor scores may be useful to assess cognitive impairment in schizophrenic patients using WCST while avoiding problems from multiple comparisons ' is ambiguous and I cannot understand what authors are trying to highlight !

Thank you very much for your comments. We revised the sentence in order to help readers to understand better.

Revised manuscript (Page 4, Line 7-9): Conclusions in Abstract

“Using WCST factor scores may reduce the possibility of type I errors due to multiple comparisons.”

Revised manuscript (Page 5, Line 13-14): Key messages

“Using WCST factor scores may reduce the possibility of type I errors due to multiple comparisons.”

Revised manuscript (Page 16, Line 8-10): Discussion

“In assessment of cognitive function in patients with schizophrenia, using the WCST factor scores may reduce the possibility of type I errors due to multiple comparisons.”

Revised manuscript (Page 17, Line 8-10): Discussion

“WCST factor scores calculated by principal component analysis may be useful for reducing the possibility of type I errors due to multiple comparisons.”

Wisconsin Card Sorting Test Scores and Clinical and Socio-demographic Correlates in Schizophrenia: Multiple Logistic Regression Analysis

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KEY WORDS:

Logistic Models, Neurobehavioral Manifestations, Neuropsychological Tests, Schizophrenia

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3722 words

ABSTRACT

Objectives: This study investigated what clinical and socio-demographic factors affected Wisconsin Card Sorting Test (WCST) factor scores of patients with schizophrenia to evaluate parameters or items of the WCST.

Design: Cross-sectional study

Setting: Patients with schizophrenia from three hospitals participated.

Participants: Participants were recruited from July 2009 to August 2011. 131 Japanese patients with schizophrenia (84 males and 47 females, 43.5±13.8 years (mean ± SD)) entered and completed the study. Participants were recruited in the study if they 1) met DSM-IV criteria for schizophrenia; 2) were physically healthy; and 3) had no mood disorders, substance abuse, neurodevelopmental disorders, epilepsy, or mental retardation. We examined their basic clinical and socio-demographic factors (sex, age, education years, age of onset, duration of illness, chlorpromazine equivalent doses, and the Positive and Negative Syndrome Scale [PANSS] scores).

Interventions: -

Primary and secondary outcome measures: All patients carried out the WCST Keio version. Five indicators were calculated, including Categories Achieved (CA), Perseverative Errors in Milner (PEM) and Nelson (PEN), Total Errors (TE), and Difficulties of Maintaining Set (DMS). From the principal component analysis, we identified two factors (1 and 2). We assessed the relationship between these factor scores and clinical and socio-demographic

factors, using multiple logistic regression analysis.

Results: Factor 1 was mainly composed of CA, PEM, PEN, and TE. Factor 2 was mainly composed of DMS. The factor 1 score was affected by age, education years, and the PANSS negative scale score. The factor 2 score was affected by duration of illness.

Conclusions: Age, education years, PANSS negative scale score and duration of illness affected WCST factor scores in patients with schizophrenia. Using WCST factor scores may reduce the possibility of type I errors due to multiple comparisons.

Trial registration: -

ARTICLE SUMMARY

Article focus

- To investigate relationships between Wisconsin Card Sorting Test (WCST) factor scores and clinical and socio-demographic factors in Japanese patients with schizophrenia using multiple logistic regression analysis
- To show distribution of each WCST score for patients with schizophrenia

Key messages

- Age, education years, Positive and Negative Syndrome Scale (PANSS) negative scale score, and duration of illness affected two WCST factor scores.
- Using WCST factor scores may reduce the possibility of type I errors due to multiple comparisons.

Strengths and limitations of this study

- We conducted principal component analysis and identified two WCST factors. Components of two WCST factors in this study were similar to previous studies.
- This is the first study to investigate relationships between WCST factor scores and clinical and socio-demographic factors in patients with schizophrenia.
- We identified a clinical and socio-demographic factor (duration of illness) that affected the WCST factor 2 score. This is a new finding.

INTRODUCTION

Cognitive impairment in patients with schizophrenia has been evaluated as an indicator of outcome regarding social functioning and quality of life.[1 2] It is reported that cognitive performance in patients with schizophrenia declines from prodrome to onset of schizophrenia (first episode).[3] Moreover, it is reported that decline of cognitive performance exists before onset of schizophrenia.[3] Many studies using brain imaging suggest that neurobiological changes in the brain are related to the cognitive impairment in schizophrenia.[4-6] Therefore, some researchers regard cognitive impairment, rather than positive and negative symptoms, as the core pathology of schizophrenia.[7]

However, there are several problems when analyzing cognitive impairment in schizophrenia. First, positive and negative syndromes modify cognitive performance.[8 9] Second, intelligence level, intelligence profile (verbal IQ and performance IQ), and educational level could affect cognitive impairment in patients with schizophrenia.[10-12] In brief, many factors have the potential to affect cognitive impairment in patients with schizophrenia. It is necessary to clarify the relationship between cognitive performance in patients with schizophrenia and clinical and socio-demographic factors in order to investigate what factors affect cognitive impairment in patients with schizophrenia.

Many neurocognitive tests have been used in order to evaluate cognitive performance in schizophrenia. The Wisconsin Card Sorting Test (WCST) is a neurocognitive test using cards and is one of the most frequently used executive

function measures.[13] A functional brain imaging study showed widespread activation across frontal and non-frontal brain regions during WCST performance.[14] It has been reported that each WCST score was related with social functioning in patients with schizophrenia.[15-17]

Recent reports suggest that WCST performance may decline during disease progression from prodrome to onset of schizophrenia. A steady (nonsignificant) progression of impairment on WCST Perseverative Errors (PE) was demonstrated from basic symptom at-risk (BS), ultra high-risk (UHR), and first-episode (FE) groups (BS: z=−0.74; UHR: z=−0.88; FE: z=−0.97).[3] However, negative and depressive symptoms may modify WCST performance in patients with schizophrenia,[9 18] and many other factors (for example, premorbid IQ) may modify WCST scores.[11]

Factor structures of WCST in patients with schizophrenia have been investigated using principal component analysis and factor analysis of WCST scores.[19-21] Differences in cognitive performance of WCST scores (Categories Achieved (CA) and PE) were shown between patients with schizophrenia and healthy controls (Cohens' d=0.91 and 0.53) in one meta-analysis, but age, education years, and other clinical and socio-demographic factors were not matched in the statistical analysis.[10] In another previous study, age and education years affected CA and PE scores.[22] In a different study, age affected PE score but education years did not affect either CA or PE scores.[10] Additional two studies showed age of onset affected PE score [23] and the Positive and Negative Syndrome Scale (PANSS) negative scale score affected CA score in patients with schizophrenia.[9] These findings

indicate that it is important to consider all clinical and socio-demographic factors to clarify which affect WCST scores in patients with schizophrenia.

In previous studies, the Wechsler Adult Intelligence Scale (WAIS) Full Scale IQ (FSIQ) showed significant correlations (P<0.05) with CA, Perseverative Errors in Milner (PEM), and Nelson (PEN) and TE scores, while items 3 and 16 of the Brief Psychiatric Rating Scale (BPRS) showed significant correlations (P<0.05) with CA, PEN and TE scores.[24] Affective flattening & blunting and avolition-apathy on the Scale for the Assessment of Negative Symptoms (SANS) showed significant correlations (P<0.05) with CA, PEM, PEN, TE and Difficulties of Maintaining Set (DMS) scores of Wisconsin Card Sorting Test Keio version (KWCST) in Japanese patients with schizophrenia (n=33).[24] However, there is no previous study that investigated other clinical and socio-demographic factors (except IQ and negative symptoms) affecting KWCST scores. Therefore, we investigated clinical and socio-demographic factors affecting scores of KWCST [25] (Japanese computerized version [26]) in Japanese patients with schizophrenia.

METHODS AND PROCEDURES

Participants

The study included 131 unrelated Japanese patients with schizophrenia (age 43.5±13.8 (mean ± SD), 84 males and 47 females) from three hospitals. The recruitment took place from both the outpatient department and the acute /

chronic wards in three hospitals. 51 outpatients (15 acute phase patients and 36 chronic phase patients) and 55 inpatients (37 acute phase patients and 18 chronic phase patients) were recruited. 25 patients were unspecified (outpatients or inpatients: 20 acute phase patients and 5 chronic phase patients). Participants were recruited from July 2009 to August 2011. Profiles of all the patients are shown in Table 1. 104 patients (78%) were receiving concomitant medications, which could include benzodiazepines, barbiturates, anticholinergics, mood stabilizers, and antidepressants.

This study protocol was approved by Nagoya University Graduate School of Medicine and Nagoya University Hospital Ethics Review Committee, and written informed consent was obtained from each participant. Participants were recruited for the study if they 1) met DSM-IV criteria for schizophrenia; 2) were physically healthy; and 3) had no mood disorders, substance abuse, neurodevelopmental disorders, epilepsy, or mental retardation. Consensus diagnoses were made by at least two experienced psychiatrists according to DSM-IV criteria on the basis of unstructured interviews with patients with schizophrenia (or their family members) and review of patients' medical records. Less than 5% of participants were excluded due to a lack of consensus. All subjects were unrelated to each other and lived in the central area of the mainland of Japan. A general characterization and psychiatric assessment of the subjects is available elsewhere.[27-29]

Measurement Settings

The WCST mainly assesses executive function, including cognitive

flexibility in response to feedback.[30] KWCST is the Japanese version of the WCST modified by Kashima.[25] KWCST consists of a card version and a computerized version, both of which have been used to investigate cognitive performance in patients with schizophrenia.[31 32] In KWCST, there are two levels of instruction.[33] The subject is told that, at the first level, this is a test of classification based on any of the three categories of color, shape, or number, and that, at the second level, the tester's categories change when the subject continues to get correct answers at fixed times. The computerized version uses instruction through letters on the monitor and the synthetic sound of the computer in order to prevent potential bias derived from a confrontation test. We selected specific indicators (CA, PEM, PEN, TE and DMS) of KWCST in this analysis, given that these indicators were investigated in previous studies.[31 32] The computerized program investigates these indicators at the second level only if the CA score at the first level is equal or less than 3. We got data for the following five indicators [32 34] at the first and second levels in this study.

(1) CA: the number of categories for which six consecutive correct responses are achieved (maximum CA is 8).

(2) PEM: the number of incorrect responses in the same category as the immediately preceding correct response after the tester's categories change (maximum PEM is 47).

(3) PEN: the number of incorrect responses in the same category as the immediately preceding incorrect response (maximum PEN is 47).

(4) TE: the total number of incorrect responses (maximum TE is 48).

(5) DMS: the number of times an incorrect response occurs after 2 to 5

consecutive correct responses (maximum DMS is 16).

We analyzed KWCST (Japanese computerized version [26]) (Shimane University, Shimane, Japan) scores at the first level of the patients with schizophrenia. Psychiatrists in three hospitals performed the KWCST assessment.

Clinical and socio-demographic factors

We investigated sex, age, education years, age of onset, duration of illness, chlorpromazine equivalent doses, and PANSS scores as clinical and socio-demographic factors. Sex was determined by patients' self-reports. Age was calculated based on the day we evaluated KWCST scores. Education years were calculated from elementary school entrance to the graduation or dropout of the last institution of higher education, which consisted of junior high school, senior high school, vocational school, junior college, university and graduate school. Age of onset was the age at onset of schizophrenia in each patient and was based on review of medical records. Duration of illness was defined from age of onset to age at the time of study. Chlorpromazine (CPZ) equivalent doses were the identified dose ratios of each antipsychotic in relation to 100 mg of chlorpromazine.[35] CPZ equivalent doses in this study were calculated based on the method by Inagaki and Inada.[36 37] PANSS is a standardized scale for evaluating positive and negative symptoms of schizophrenia and was used to evaluate severity of schizophrenia in the patients.[38]

Statistical analysis

Clinical profiles of the patients with schizophrenia are shown in Table 1. We investigated correlations of the five indicators of the KWCST (CA, PEM, PEN, TE and DMS) in patients with schizophrenia by Spearman's Rank Correlation Test.

Principal component analysis

WCST factors were identified by principal component analysis of the five indicators without rotation. Factors were retained using the eigenvalue >1 criterion.

Main analysis

In the main analysis, we investigated what clinical and socio-demographic factors affected WCST factor scores in a multiple logistic regression analysis. Our reasoning for not using multiple linear regression is explained in Information S1 (Web only file). The dependent variables were WCST factor scores and independent variables were the following candidate clinical and socio-demographic factors: sex, age, education years, age of onset, duration of illness, CPZ equivalent doses, and PANSS (positive, negative and general psychopathology scale) scores. We made a dummy conversion variable (1 or 0) for sex. We converted factor scores into categorical variables (1 or 0), using cutoff values that were median values of the factor scores. The median was chosen as a cutoff point for dependent variables based on reasons explained in Information S2 (Web only file). In our multiple logistic regression analysis, we did additional two tests. First, we did an omnibus test of model

coefficients versus a model with intercept only. This test detects whether a model is significant (P<0.05) or not; this is a test of the null hypothesis that adding any variables to the model has not significantly increased our ability to predict the dependent variable. A model is useless if the P-value in omnibus test was >0.05. Second, we did a Hosmer and Lemeshow goodness of fit test, which shows how well the model fits the data with P>0.05 indicating good fit; this is a test of the null hypothesis that there is a linear relationship between the predictor variables and the log odds of the criterion variable. The hit rate in multiple logistic regression analysis is a measure how well a model predicts the dependent variable.

Sub-analysis

In the sub-analysis, we also investigated what clinical and socio-demographic factors affected the five indicators of WCST in the multiple logistic regression analysis. We used multiple logistic regression analysis in the sub-analysis in order to compare the results between main and sub-analysis. In this analysis, the dependent variables were the five indicators of WCST and independent variables were the candidate clinical and socio-demographic factors. We compared the results of the multiple logistic regression analysis with the results of previous studies.[9 10 23]

Software

IBM SPSS statistical software (IBM Japan, Tokyo, Japan), version 19 was used for analyses. The significance level was set at P=0.05 using a

two-tailed t-test.

RESULTS

Distribution of the WCST (CA, PEM, PEN, TE and DMS) scores in patients with schizophrenia is shown in Figure 1. The numbers of patients in the following analyses were CA *n*=131, PEM *n*=122, PEN *n*=131, TE *n*=115 and DMS *n*=131 because of missing values in the data.

Spearman's rank correlation coefficients between the five indicators of WCST are shown in Table 2. Although no strong correlation (>0.8) was observed in any of these clinical and socio-demographic factors, the Spearman's correlation between PANSS negative scale score and PANSS general psychopathology scale score was high (0.74).

Principal component analysis

Two factors (1 and 2) were identified in principal component analysis of the five indicators of WCST. Factor 1 mainly consisted of CA, PEM, PEN, and TE, and accounted for 65.6% of the total variance. Factor 2 mainly consisted of DMS and accounted for 23.2% of the total variance (Table 3 and Figure 2). We converted the factor 1 and factor 2 scores into categorical variables (1 or 0) using cutoff values. The cutoff values were the median values (factor 1: -0.299; factor 2: 0.080). We used these categorical variables as dependent variables in multiple logistic regression analysis.

Main analysis

Age, education years, and PANSS negative scale score significantly affected factor 1 score, and the duration of illness significantly affected factor 2 score in patients with schizophrenia (Table 4). The details of the results from the multiple logistic regression analyses are shown in Table S1 (Web only file). *P*-values in an omnibus test of model coefficients versus a model with intercept only were statistically significant ($P<0.05$) for all the models in WCST factor scores. In the Hosmer and Lemeshow goodness of fit test, all the models fit the data adequately with $P>0.05$. Factor 1 score may be predicted precisely by this model considering hit rate (0.77).

CPZ equivalent doses did not affect the WCST scores. PANSS positive scale score did not affect the WCST scores; whereas PANSS negative scale score did.

Sub-analysis

In the sub-analyses, age, education years, and PANSS negative scale score significantly affected CA score. Age and education years significantly affected PEM, PEN, and TE scores, and age significantly affected DMS score in patients with schizophrenia. The details of these results are shown in Table S2 and Table S3 (Web only file); Table S3 includes the results of previous studies. *P*-values in the omnibus test of model coefficients versus a model with intercept only were statistically significant ($P<0.05$) for all the models for each WCST score, and all the models fit the data adequately in the Hosmer and Lemeshow goodness of fit test.

DISCUSSION

This study is the first to investigate the relationships between WCST factor scores and clinical and socio-demographic factors in Japanese patients with schizophrenia by multiple logistic regression analysis. We showed the distribution of each WCST score (Figure 1). We conducted principal component analysis and identified two factors. The components of these two factors were similar to previous studies.[19-21] Thus, we could reduce the number of WCST outcomes from five indicators to two factors (Table 3). In assessment of cognitive function in patients with schizophrenia, using the WCST factor scores may reduce the possibility of type I errors due to multiple comparisons. We analyzed the relationship between these two factors and clinical and socio-demographic factors with multiple logistic regression analysis. We found that age, education years, PANSS negative scale score, and duration of illness affected the two WCST factor scores.

Principal component analysis

Our study showed that factor 1 mainly consisted of CA, PEM, PEN, and TE and factor 2 mainly consisted of DMS. In the previous studies with principal component analysis and factor analysis of WCST scores in patients with schizophrenia, Categories Complete (CC) (an indicator examining numbers of categories achieved in the same way as CA), PE (an indicator examining perseveration in the same way as PEM and PEN) and TE mainly constituted one factor. Failure to Maintain Set (FMS) (an indicator examining difficulty of maintaining set, similar to DMS) mainly constituted another factor.[19-21] Our

results resembled the results of the principal component analysis and factor analysis of WCST in these previous studies.[19-21]

Factor 1, which included representative indicators (CC, PE, etc.), was named as 'general executive functioning' in a previous study.[21] Therefore, factor 1 in our study also may represent general executive functioning. In our study, factor 1 score showed a high contribution ratio of the total variance (65.6%) in principal component analysis of WCST scores in patients with schizophrenia. WCST factor scores calculated by principal component analysis may be useful for reducing the possibility of type I errors due to multiple comparisons.

Factor 1 and factor 2 in our study resembled those in previous studies.[19-21] Therefore, the KWCST measures cognitive function similarly to the traditional WCST.

Main analysis

We identified clinical and socio-demographic factors (age, education years, and PANSS negative scale score) affecting WCST factor 1 score. We also identified a clinical and socio-demographic factor (duration of illness) affecting WCST factor 2 score. This is an important new finding. Comparing the three main previous studies [9 10 23] with the current study, we summarized shared and different findings, shown in Table 4.

The shared findings were that age and PANSS negative scale score were related to WCST scores (Table 4).[9 10 23]

Two findings differed from previous studies (Table 4).[9 10 23] First, we

found a new relationship between education years and WCST scores. Second, we found no relationship between age of onset and WCST scores. Differences in the results between previous studies [9 10 23] and our study may be explained by differences of ethnicity, distribution of age and education years, types of statistical analysis used, and the version of WCST. These differences suggest that future studies about WCST should be conducted with attention to these conditions.

CPZ equivalent doses did not affect the WCST scores in this study. This result was in the same direction as one meta-analysis (n=4524) though recent studies had suggested the possibility of an effect.[31 39 40] Future studies will be necessary to clarify whether CPZ equivalent doses affect WCST scores under other conditions.

PANSS positive scale score did not affect the WCST scores but the PANSS negative scale score did. A recent meta-analysis (n=6519) suggested that negative symptoms related to cognitive performance in patients with schizophrenia whereas positive symptoms did not.[41] This suggests that the relationships between PANSS positive and negative scale scores and WCST scores in this study may be reasonable.

Sub-analysis

We found that factor 1 score and factor 1 score's main components (CA, PEM, PEN and TE) related to age and education years (Table S4 (Web only file)).

The effect of duration of illness on WCST factor 2 score, which was mainly influenced by DMS, is the novel finding of the main analysis. However, DMS is not significantly associated with the duration of illness in the sub-analysis (Table S4 (Web only file)). This discrepancy between the main analysis and sub-analysis may be derived from the difference between DMS and factor 2 (Factor 2 included not only DMS, but also CA, PEM, PEN and TE).

Limitations

There are several limitations in this study. First, other clinical and socio-demographic factors that were not investigated in the current study could affect WCST scores. Candidates for such clinical and socio-demographic factors are IQ,[42] participants' dominant arm, experience with using a computer, doses of drugs affecting cognitive performance (anticholinergics, benzodiazepines, etc), sleep,[43] eating, and risk factors of arteriosclerosis (BMI, blood pressure, etc).[44] It may be useful to include these factors in future studies. Second, the WCST indicators (CA, PEM, PEN, TE and DMS scores) in our study did not cover all WCST indicators; we selected the major five indicators. We might find other factors by principal component analysis or new relationships between new WCST factors and clinical and socio-demographic factors if we included other clinical indicators. Third, we dichotomized continuous variables (WCST factor scores) in the multiple logistic regression analysis. Therefore, careful interpretation of the results may be needed, considering the statistical weak points of dichotomizing continuous variables.[45]

Conclusion

This study is the first study that investigated clinical and socio-demographic factors affecting WCST factor scores calculated by principal component analysis in patients with schizophrenia. The study was conducted in a relatively large Japanese population. We showed distribution of measured five WCST indicators in patients with schizophrenia and confirmed two WCST factors by principal component analysis. Age, education years, PANSS negative scale score and duration of illness affected WCST scores in patients with schizophrenia. The interaction between the duration of illness and a factor of the WCST needs further confirmation in future studies because there was a discrepancy between the results of the main analysis and the sub-analysis in this study.

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FOOTNOTES

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Competing interests

None

Ethics approval

This study was approved under the guidelines for epidemiological studies by the Nagoya University Graduate School of Medicine and Nagoya University Hospital Ethics Review Committee and was conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from each subject before the start of the study.

Contributors

MB, TKo and NO conceived and designed the experiments. MB, TKo, TKi, KK and YA performed the experiments. MB, TKo, BA, TO, NK, TI and NO analyzed the data. MB, TKo and YA contributed reagents/materials/analysis tools. MB, TKo, TO, BA and NO wrote the paper.

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Data sharing statement

No additional data are available.

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FIGURE LEGENDS

Figure 1. Distribution of WCST scores in patients with schizophrenia (*n*=131)

None of the distribution was normal distribution.

Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set

[a]. Standard deviation

[b]. % of cases

Figure 2. Component plot in principal component analysis of WCST scores in patients with schizophrenia (*n*=131)

Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set

Table 1. Profiles of patients with schizophrenia

Table 2. Correlation coefficients for WCST scores in patients with schizophrenia

Table 3. Factor loadings in principal component analysis in patients with schizophrenia (*n*=131)

Table 4. Clinical and socio-demographic factors for WCST scores of patients with schizophrenia in the current study (main analysis) and for previous studies

APPENDICES

Table S1 (Web only file). Multiple logistic regression analysis of WCST factor scores in patients with schizophrenia (*n*=131)

Table S2 (Web only file). Multiple logistic regression analysis of WCST scores in patients with schizophrenia (*n*=131)

Table S3 (Web only file). Clinical and socio-demographic factors for WCST scores of patients with schizophrenia in this study (sub-analysis) and previous studies

Table S4 (Web only file). Clinical and socio-demographic factors for WCST scores of patients with schizophrenia in this study (main analysis and sub-analysis)

Information S1 (Web only file). Why we did not use multiple linear regression analysis in this study.

Information S2 (Web only file). Why we used the median as a cutoff point for dependent variables (WCST factor scores) in the multiple logistic regression analysis.

Table 1. Profiles of patients with schizophrenia

		Patients with schizophrenia (*n* =131)	
Sex		Male	Female
		84	47
		Average	(SD[a])
Age (y)		43.5	(13.8)
Education (y)		12.4	(2.4)
Age of onset (y)		26.3	(10.0)
Duration of illness (y)		17.0	(12.8)
Chlorpromazine equivalent doses (mg)		618.4	(391.1)
PANSS scale	Positive (7-49)	16.5	(5.3)
	Negative (7-49)	19.3	(5.6)
	General (16-112)	36.6	(9.4)
	Total (30-210)	72.4	(18.1)

[a]. Standard deviation

Table 2. Correlation coefficients for WCST scores in patients with schizophrenia

		Patients with schizophrenia (n=131)				
		CA	PEM	PEN	TE	DMS
correlation coefficient[a]	CA	-	-	-	-	-
	PEM	-0.70**	-	-	-	-
	PEN	-0.79**	0.73**	-	-	-
	TE	-0.88**	0.71**	0.89**	-	-
	DMS	-0.58**	0.30*	0.28*	0.30*	-

*: P<0.01, **: P<0.001

Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set

[a]. Spearman's rank correlation coefficient

Table 3. Factor loadings in principal component analysis in patients with schizophrenia (*n*=131)

		factor 1	factor 2
WCST score	CA	-0.89	0.36
	PEM	0.84	0.27
	PEN	0.92	0.27
	TE	0.93	0.13
	DMS	0.29	-0.93
Variance (%) explained by each factor		65.6	23.2
Cumulative explained variance (%)		65.6	88.9

Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set

Factor analysis was based on principal component method without rotation.

Two factors were retained using the eigenvalue >1 criterion.

Table 4. Clinical and socio-demographic factors for WCST scores of patients with schizophrenia in the current study (main analysis) and for previous studies

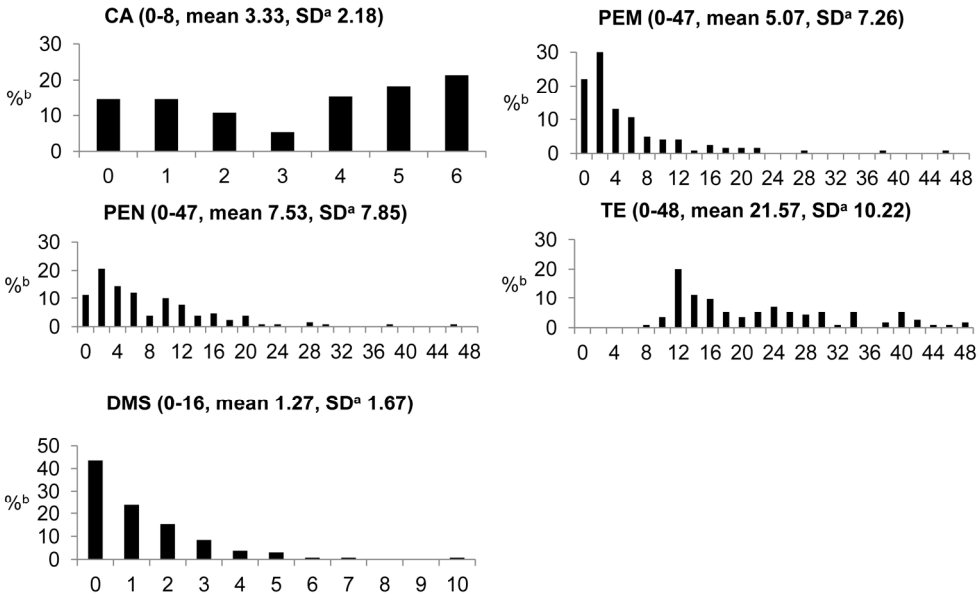
	Patients with schizophrenia (*n* =131) Main analysis		Previous studies		
	Factor 1 score	Factor 2 score	CA[a]	PE[a]	TE[a]
Sex			n/a	n/a	n/a
Age	***		n.s.[b]	○[b]	n/a
Education years	**		n.s.[b]	n.s.[b]	n/a
Age of onset			n.s.[c]	○[c]	n/a
Duration of illness		*	n.s.[b]	n.s.[b]	n/a
Chlorpromazine equivalent doses			n/a	n/a	n/a
PANSS score positive (7-49)			n.s.[d]	n/a	n/a
PANSS score negative (7-49)	*		○[d]	n/a	n/a
PANSS score general (16-112)			n.s.[d]	n/a	n/a
hit rate	0.77	0.58	n/a	n/a	n/a

*: *P*<0.05, **: *P*<0.01, ***: *P*<0.001

Abbreviations: CA, Categories Achieved; PE, Perseverative errors; TE, Total Errors; n/a, data not available; n.s., not significant

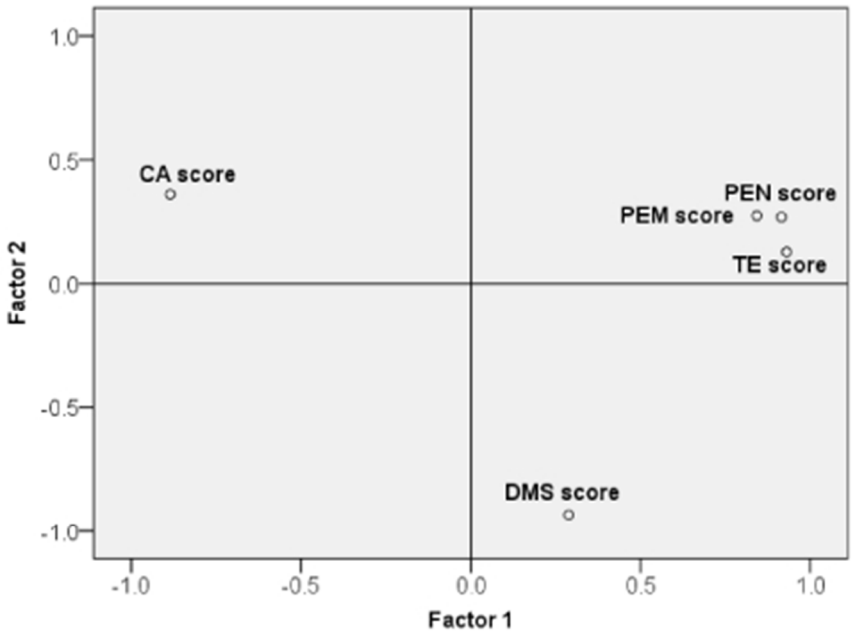
[a]. CA, PE and TE were included in factor 1 in a previous study.

[b]. Reference 10, [c]. Reference 23, [d]. Reference 9



None of the distribution was normal distribution.
Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set
[a]. Standard deviation
[b]. % of cases

169x104mm (300 x 300 DPI)



Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set
36x27mm (300 x 300 DPI)

Table S1. Multiple logistic regression analysis of WCST factor scores in patients with schizophrenia (*n*=131)

Forward-backward stepwise selection, Setting: P_{in}=0.05, P_{out}=0.1								
		Factor 1 score				Factor 2 score			
		B[a]	Exp(B)[b]	95% CI[c]	*P*-value	B[a]	Exp(B)[b]	95% CI[c]	*P*-value
Sex (Male 1, Female 0)		-	-	-	-	-	-	-	-
Age (y)		0.06	1.06	1.03-1.10	**<0.001**	-	-	-	-
Education (y)		-0.39	0.68	0.54-0.85	**0.001**	-	-	-	-
Age of onset (y)		-	-	-	-	-	-	-	-
Duration of illness (y)		-	-	-	-	-0.03	0.97	0.94-1.00	**0.03**
CPZeq (mg/day)		-	-	-	-	-	-	-	-
PANSS score	Positive (7-49)	-	-	-	-	-	-	-	-
	Negative (7-49)	0.11	1.12	1.02-1.22	**0.01**	-	-	-	-
	General (16-112)	-	-	-	-	-	-	-	-
Intercept		-0.03	0.97	-	0.98	0.55	1.73	-	0.08
omnibus test		***P*<0.001**				**0.02**			
Hosmer and Lemeshow test		0.12				0.85			
hit rate		0.77				0.58			

Abbreviations: CPZeq, Chlorpromazine equivalent doses

[a]. Regression coefficient

[b]. This is the exponentiation of the B coefficient, which is an odds ratio.

[c]. Confidence interval of Exp(B)

Cutoff values were factor 1: -0.299, factor 2: 0.080.

0 and 1 are dummy variables in respect to subjects' sex.

Considering omnibus test *P*-values, these models are significant (*P*<0.05).

Considering Hosmer and Lemeshow test *P*-values (*P*>0.05), factor 1 score and factor 2 score may be predicted by this model.

Table S2. Multiple logistic regression analysis of WCST scores in patients with schizophrenia (*n*=131)

		Forward-backward stepwise selection, Setting: P_{in}=0.05, P_{out}=0.1																			
		CA				PEM				PEN				TE				DMS			
		B[a]	Exp(B)[b]	95% CI[c]	*P*-value	B[a]	Exp(B)[b]	95% CI[c]	*P*-value	B[a]	Exp(B)[b]	95% CI[c]	*P*-value	B[a]	Exp(B)[b]	95% CI[c]	*P*-value	B[a]	Exp(B)[b]	95% CI[c]	*P*-value
Sex (Male 1, Female 0)		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Age (y)		-0.06	0.94	0.92-0.97	**<0.001**	0.03	1.03	1.00-1.06	**0.04**	0.05	1.05	1.02-1.08	**0.001**	0.06	1.06	1.03-1.10	**<0.001**	0.03	1.03	1.01-1.06	**0.02**
Education (y)		0.31	1.36	1.13-1.64	**0.001**	-0.33	0.72	0.59-0.87	**0.001**	-0.19	0.83	0.70-0.97	**0.02**	-0.35	0.70	0.57-0.87	**0.001**	-	-	-	-
Age of onset (y)		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Duration of illness (y)		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CPZeq (mg/day)		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PANSS score	Positive (7-49)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Negative (7-49)	-0.08	0.92	0.85-0.99	**0.03**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	General (16-112)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Intercept		0.52	1.68	-	0.72	3.21	24.70	-	**0.02**	0.37	1.45	-	0.76	1.76	5.79	-	0.22	-1.12	0.33	-	0.07
omnibus test		***P*<0.001**				***P*<0.001**				***P*<0.001**				***P*<0.001**				**0.02**			
Hosmer and Lemeshow test		0.44				0.76				0.56				0.56				0.88			
hit rate		0.69				0.66				0.62				0.71				0.60			

Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set; CPZeq, Chlorpromazine equivalent doses

[a]. Regression coefficient

[b]. This is the exponentiation of the B coefficient, which is an odds ratio.

[c]. Confidence interval of Exp(B)

Cutoff values were CA: 4, PEM: 2, PEN: 5, TE: 18, DMS: 1.

0 and 1 are dummy variables in respect to subjects' sex.

Considering omnibus test *P*-values, these models are significant (*P*<0.05).

Considering Hosmer and Lemeshow test *P*-values (0.05<*P*), CA, PEN, PEM, TE and DMS scores may be predicted by this model.

Table S3. Clinical and socio-demographic factors for WCST scores of patients with schizophrenia in this study (sub-analysis) and previous studies

	Patients with schizophrenia (*n* =131) Sub-analysis					Previous studies		
	CA	PEM	PEN	TE	DMS	CA	PE	TE
Sex						n/a	n/a	n/a
Age	***	*	**	***	*	n.s.[b]	○[b]	n/a
Education years	**	**	*	**		n.s.[b]	n.s.[b]	n/a
Age of onset						n.s.[c]	○[c]	n/a
Duration of illness						n.s.[b]	n.s.[b]	n/a
Chlorpromazine equivalent doses						n/a	n/a	n/a
PANSS score positive (7-49)						n.s.[d]	n/a	n/a
PANSS score negative (7-49)	*					○[d]	n/a	n/a
PANSS score general (16-112)						n.s.[d]	n/a	n/a
hit rate	0.69	0.66	0.62	0.71	0.60	n/a	n/a	n/a

*: $P<0.05$, **: $P<0.01$, ***: $P<0.001$

Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set; PE, Perseverative errors; n/a, data not available; n.s., not significant

[a]. Reference 10

[b]. Reference 23

[c]. Reference 9

Table S4. Clinical and socio-demographic factors for WCST scores of patients with schizophrenia in this study (main analysis and sub-analysis)

		Patients with schizophrenia (*n* =131)						
		Main analysis		Sub-analysis				
		Factor 1 score	Factor 2 score	CA[a]	PEM[a]	PEN[a]	TE[a]	DMS[b]
Sex								
Age		***		***	*	**	***	*
Education years		**		**	**	*	**	
Age of onset								
Duration of illness			*					
Chlorpromazine equivalent doses								
PANSS score	positive (7-49)							
	negative (7-49)	*		*				
	general (16-112)							
hit rate		0.77	0.58	0.69	0.66	0.62	0.71	0.60

*: *P*<0.05, **: *P*<0.01, ***: *P*<0.001

Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set

[a]. CA, PEM, PEN and TE were included in factor 1 in this study.

[b]. DMS was included in factor 2 in this study.

Information S1. Why we did not use multiple linear regression analysis in this study.

We chose multiple logistic regression because of the distribution of the dependent variables (WCST factor scores). To conduct multiple linear regression analysis, normality of dependent variables is needed.[1] The distribution of the dependent variables (WCST factor scores) in this study was not normal because the *P*-values of two kinds of normality tests (Kolmogorov-Smirnov test and Shapiro-Wilk test) were less than 0.001. We also tested normality of the logarithmic distribution of the dependent variables (WCST factor scores); the *P*-values on both types of normality test (Kolmogorov-Smirnov test and Shapiro-Wilk test) were less than 0.001. Therefore, we used multiple logistic regression which can analyze variables in non-normality.[2]

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Information S2. Why we used the median as a cutoff point for dependent variables (WCST factor scores) in the multiple logistic regression analysis.

There were two reasons that we used the median as a cutoff point for the dependent variables (WCST factor scores) in our multiple logistic regression analysis. First, a previous psychiatric research report used the median as a cutoff point in dependent variables for multiple logistic regression analysis.[1] Second, the most common approach for dichotomizing continuous variables was to take the sample median because there were no cutoff points of WCST factor scores in previous studies.[2]

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Wisconsin Card Sorting Test Scores and Clinical and Socio-demographic Correlates in Schizophrenia: Multiple Logistic Regression Analysis

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ABSTRACT

Objectives: This study investigated what clinical and socio-demographic factors affected Wisconsin Card Sorting Test (WCST) factor scores of patients with schizophrenia to evaluate parameters or items of the WCST.

Design: Cross-sectional study

Setting: Patients with schizophrenia from three hospitals participated.

Participants: Participants were recruited from July 2009 to August 2011. 131 Japanese patients with schizophrenia (84 males and 47 females, 43.5±13.8 years (mean ± SD)) entered and completed the study. Participants were recruited in the study if they 1) met DSM-IV criteria for schizophrenia; 2) were physically healthy; and 3) had no mood disorders, substance abuse, neurodevelopmental disorders, epilepsy, or mental retardation. We examined their basic clinical and socio-demographic factors (sex, age, education years, age of onset, duration of illness, chlorpromazine equivalent doses, and the Positive and Negative Syndrome Scale [PANSS] scores).

Interventions: -

Primary and secondary outcome measures: All patients carried out the WCST Keio version. Five indicators were calculated, including Categories Achieved (CA), Perseverative Errors in Milner (PEM) and Nelson (PEN), Total Errors (TE), and Difficulties of Maintaining Set (DMS). From the principal component analysis, we identified two factors (1 and 2). We assessed the relationship between these factor scores and clinical and socio-demographic

factors, using multiple logistic regression analysis.

Results: Factor 1 was mainly composed of CA, PEM, PEN, and TE. Factor 2 was mainly composed of DMS. The factor 1 score was affected by age, education years, and the PANSS negative scale score. The factor 2 score was affected by duration of illness.

Conclusions: Age, education years, PANSS negative scale score and duration of illness affected WCST factor scores in patients with schizophrenia. Using WCST factor scores may reduce the possibility of type I errors due to multiple comparisons.

Trial registration: -

ARTICLE SUMMARY

Article focus

- To investigate relationships between Wisconsin Card Sorting Test (WCST) factor scores and clinical and socio-demographic factors in Japanese patients with schizophrenia using multiple logistic regression analysis
- To show distribution of each WCST score for patients with schizophrenia

Key messages

- Age, education years, Positive and Negative Syndrome Scale (PANSS) negative scale score, and duration of illness affected two WCST factor scores.
- Using WCST factor scores may reduce the possibility of type I errors due to multiple comparisons.

Strengths and limitations of this study

- We conducted principal component analysis and identified two WCST factors. Components of two WCST factors in this study were similar to previous studies.
- This is the first study to investigate relationships between WCST factor scores and clinical and socio-demographic factors in patients with schizophrenia.
- We identified a clinical and socio-demographic factor (duration of illness) that affected the WCST factor 2 score. This is a new finding.

INTRODUCTION

Cognitive impairment in patients with schizophrenia has been evaluated as an indicator of outcome regarding social functioning and quality of life.[1 2] It is reported that cognitive performance in patients with schizophrenia declines from prodrome to onset of schizophrenia (first episode).[3] Moreover, it is reported that decline of cognitive performance exists before onset of schizophrenia.[3] Many studies using brain imaging suggest that neurobiological changes in the brain are related to the cognitive impairment in schizophrenia.[4-6] Therefore, some researchers regard cognitive impairment, rather than positive and negative symptoms, as the core pathology of schizophrenia.[7]

However, there are several problems when analyzing cognitive impairment in schizophrenia. First, positive and negative syndromes modify cognitive performance.[8 9] Second, intelligence level, intelligence profile (verbal IQ and performance IQ), and educational level could affect cognitive impairment in patients with schizophrenia.[10-12] In brief, many factors have the potential to affect cognitive impairment in patients with schizophrenia. It is necessary to clarify the relationship between cognitive performance in patients with schizophrenia and clinical and socio-demographic factors in order to investigate what factors affect cognitive impairment in patients with schizophrenia.

Many neurocognitive tests have been used in order to evaluate cognitive performance in schizophrenia. The Wisconsin Card Sorting Test (WCST) is a neurocognitive test using cards and is one of the most frequently used executive

function measures.[13] A functional brain imaging study showed widespread activation across frontal and non-frontal brain regions during WCST performance.[14] It has been reported that each WCST score was related with social functioning in patients with schizophrenia.[15-17]

Recent reports suggest that WCST performance may decline during disease progression from prodrome to onset of schizophrenia. A steady (nonsignificant) progression of impairment on WCST Perseverative Errors (PE) was demonstrated from basic symptom at-risk (BS), ultra high-risk (UHR), and first-episode (FE) groups (BS: z=−0.74; UHR: z=−0.88; FE: z=−0.97).[3] However, negative and depressive symptoms may modify WCST performance in patients with schizophrenia,[9 18] and many other factors (for example, premorbid IQ) may modify WCST scores.[11]

Factor structures of WCST in patients with schizophrenia have been investigated using principal component analysis and factor analysis of WCST scores.[19-21] Differences in cognitive performance of WCST scores (Categories Achieved (CA) and PE) were shown between patients with schizophrenia and healthy controls (Cohens' d=0.91 and 0.53) in one meta-analysis, but age, education years, and other clinical and socio-demographic factors were not matched in the statistical analysis.[10] In another previous study, age and education years affected CA and PE scores.[22] In a different study, age affected PE score but education years did not affect either CA or PE scores.[10] Additional two studies showed age of onset affected PE score [23] and the Positive and Negative Syndrome Scale (PANSS) negative scale score affected CA score in patients with schizophrenia.[9] These findings

indicate that it is important to consider all clinical and socio-demographic factors to clarify which affect WCST scores in patients with schizophrenia.

In previous studies, the Wechsler Adult Intelligence Scale (WAIS) Full Scale IQ (FSIQ) showed significant correlations (P<0.05) with CA, Perseverative Errors in Milner (PEM), and Nelson (PEN) and TE scores, while items 3 and 16 of the Brief Psychiatric Rating Scale (BPRS) showed significant correlations (P<0.05) with CA, PEN and TE scores.[24] Affective flattening & blunting and avolition-apathy on the Scale for the Assessment of Negative Symptoms (SANS) showed significant correlations (P<0.05) with CA, PEM, PEN, TE and Difficulties of Maintaining Set (DMS) scores of Wisconsin Card Sorting Test Keio version (KWCST) in Japanese patients with schizophrenia (n=33).[24] However, there is no previous study that investigated other clinical and socio-demographic factors (except IQ and negative symptoms) affecting KWCST scores. Therefore, we investigated clinical and socio-demographic factors affecting scores of KWCST [25] (Japanese computerized version [26]) in Japanese patients with schizophrenia.

METHODS AND PROCEDURES

Participants

The study included 131 unrelated Japanese patients with schizophrenia (age 43.5±13.8 (mean ± SD), 84 males and 47 females) from three hospitals. The recruitment took place from both the outpatient department and the acute /

chronic wards in three hospitals. 51 outpatients (15 acute phase patients and 36 chronic phase patients) and 55 inpatients (37 acute phase patients and 18 chronic phase patients) were recruited. 25 patients were unspecified (outpatients or inpatients: 20 acute phase patients and 5 chronic phase patients). Participants were recruited from July 2009 to August 2011. Profiles of all the patients are shown in Table 1. 104 patients (78%) were receiving concomitant medications, which could include benzodiazepines, barbiturates, anticholinergics, mood stabilizers, and antidepressants.

This study protocol was approved by Nagoya University Graduate School of Medicine and Nagoya University Hospital Ethics Review Committee, and written informed consent was obtained from each participant. Participants were recruited for the study if they 1) met DSM-IV criteria for schizophrenia; 2) were physically healthy; and 3) had no mood disorders, substance abuse, neurodevelopmental disorders, epilepsy, or mental retardation. Consensus diagnoses were made by at least two experienced psychiatrists according to DSM-IV criteria on the basis of unstructured interviews with patients with schizophrenia (or their family members) and review of patients' medical records. Less than 5% of participants were excluded due to a lack of consensus. All subjects were unrelated to each other and lived in the central area of the mainland of Japan. A general characterization and psychiatric assessment of the subjects is available elsewhere.[27-29]

Measurement Settings

The WCST mainly assesses executive function, including cognitive

flexibility in response to feedback.[30] KWCST is the Japanese version of the WCST modified by Kashima.[25] KWCST consists of a card version and a computerized version, both of which have been used to investigate cognitive performance in patients with schizophrenia.[31 32] In KWCST, there are two levels of instruction.[33] The subject is told that, at the first level, this is a test of classification based on any of the three categories of color, shape, or number, and that, at the second level, the tester's categories change when the subject continues to get correct answers at fixed times. The computerized version uses instruction through letters on the monitor and the synthetic sound of the computer in order to prevent potential bias derived from a confrontation test. We selected specific indicators (CA, PEM, PEN, TE and DMS) of KWCST in this analysis, given that these indicators were investigated in previous studies.[31 32] The computerized program investigates these indicators at the second level only if the CA score at the first level is equal or less than 3. We got data for the following five indicators [32 34] at the first and second levels in this study.

(1) CA: the number of categories for which six consecutive correct responses are achieved (maximum CA is 8).

(2) PEM: the number of incorrect responses in the same category as the immediately preceding correct response after the tester's categories change (maximum PEM is 47).

(3) PEN: the number of incorrect responses in the same category as the immediately preceding incorrect response (maximum PEN is 47).

(4) TE: the total number of incorrect responses (maximum TE is 48).

(5) DMS: the number of times an incorrect response occurs after 2 to 5

consecutive correct responses (maximum DMS is 16).

We analyzed KWCST (Japanese computerized version [26]) (Shimane University, Shimane, Japan) scores at the first level of the patients with schizophrenia. Psychiatrists in three hospitals performed the KWCST assessment.

Clinical and socio-demographic factors

We investigated sex, age, education years, age of onset, duration of illness, chlorpromazine equivalent doses, and PANSS scores as clinical and socio-demographic factors. Sex was determined by patients' self-reports. Age was calculated based on the day we evaluated KWCST scores. Education years were calculated from elementary school entrance to the graduation or dropout of the last institution of higher education, which consisted of junior high school, senior high school, vocational school, junior college, university and graduate school. Age of onset was the age at onset of schizophrenia in each patient and was based on review of medical records. Duration of illness was defined from age of onset to age at the time of study. Chlorpromazine (CPZ) equivalent doses were the identified dose ratios of each antipsychotic in relation to 100 mg of chlorpromazine.[35] CPZ equivalent doses in this study were calculated based on the method by Inagaki and Inada.[36 37] PANSS is a standardized scale for evaluating positive and negative symptoms of schizophrenia and was used to evaluate severity of schizophrenia in the patients.[38]

Statistical analysis

Clinical profiles of the patients with schizophrenia are shown in Table 1. We investigated correlations of the five indicators of the KWCST (CA, PEM, PEN, TE and DMS) in patients with schizophrenia by Spearman's Rank Correlation Test.

Principal component analysis

WCST factors were identified by principal component analysis of the five indicators without rotation. Factors were retained using the eigenvalue >1 criterion.

Main analysis

In the main analysis, we investigated what clinical and socio-demographic factors affected WCST factor scores in a multiple logistic regression analysis. Our reasoning for not using multiple linear regression is explained in Information S1 (Web only file). The dependent variables were WCST factor scores and independent variables were the following candidate clinical and socio-demographic factors: sex, age, education years, age of onset, duration of illness, CPZ equivalent doses, and PANSS (positive, negative and general psychopathology scale) scores. We made a dummy conversion variable (1 or 0) for sex. We converted factor scores into categorical variables (1 or 0), using cutoff values that were median values of the factor scores. The median was chosen as a cutoff point for dependent variables based on reasons explained in Information S2 (Web only file). In our multiple logistic regression analysis, we did additional two tests. First, we did an omnibus test of model

coefficients versus a model with intercept only. This test detects whether a model is significant (P<0.05) or not; this is a test of the null hypothesis that adding any variables to the model has not significantly increased our ability to predict the dependent variable. A model is useless if the P-value in omnibus test was >0.05. Second, we did a Hosmer and Lemeshow goodness of fit test, which shows how well the model fits the data with P>0.05 indicating good fit; this is a test of the null hypothesis that there is a linear relationship between the predictor variables and the log odds of the criterion variable. The hit rate in multiple logistic regression analysis is a measure how well a model predicts the dependent variable.

Sub-analysis

In the sub-analysis, we also investigated what clinical and socio-demographic factors affected the five indicators of WCST in the multiple logistic regression analysis. We used multiple logistic regression analysis in the sub-analysis in order to compare the results between main and sub-analysis. In this analysis, the dependent variables were the five indicators of WCST and independent variables were the candidate clinical and socio-demographic factors. We compared the results of the multiple logistic regression analysis with the results of previous studies.[9 10 23]

Software

IBM SPSS statistical software (IBM Japan, Tokyo, Japan), version 19 was used for analyses. The significance level was set at P=0.05 using a

two-tailed t-test.

RESULTS

Distribution of the WCST (CA, PEM, PEN, TE and DMS) scores in patients with schizophrenia is shown in Figure 1. The numbers of patients in the following analyses were CA *n*=131, PEM *n*=122, PEN *n*=131, TE *n*=115 and DMS *n*=131 because of missing values in the data.

Spearman's rank correlation coefficients between the five indicators of WCST are shown in Table 2. Although no strong correlation (>0.8) was observed in any of these clinical and socio-demographic factors, the Spearman's correlation between PANSS negative scale score and PANSS general psychopathology scale score was high (0.74).

Principal component analysis

Two factors (1 and 2) were identified in principal component analysis of the five indicators of WCST. Factor 1 mainly consisted of CA, PEM, PEN, and TE, and accounted for 65.6% of the total variance. Factor 2 mainly consisted of DMS and accounted for 23.2% of the total variance (Table 3 and Figure 2). We converted the factor 1 and factor 2 scores into categorical variables (1 or 0) using cutoff values. The cutoff values were the median values (factor 1: -0.299; factor 2: 0.080). We used these categorical variables as dependent variables in multiple logistic regression analysis.

Main analysis

Age, education years, and PANSS negative scale score significantly affected factor 1 score, and the duration of illness significantly affected factor 2 score in patients with schizophrenia (Table 4). The details of the results from the multiple logistic regression analyses are shown in Table S1 (Web only file). *P*-values in an omnibus test of model coefficients versus a model with intercept only were statistically significant ($P<0.05$) for all the models in WCST factor scores. In the Hosmer and Lemeshow goodness of fit test, all the models fit the data adequately with $P>0.05$. Factor 1 score may be predicted precisely by this model considering hit rate (0.77).

CPZ equivalent doses did not affect the WCST scores. PANSS positive scale score did not affect the WCST scores; whereas PANSS negative scale score did.

Sub-analysis

In the sub-analyses, age, education years, and PANSS negative scale score significantly affected CA score. Age and education years significantly affected PEM, PEN, and TE scores, and age significantly affected DMS score in patients with schizophrenia. The details of these results are shown in Table S2 and Table S3 (Web only file); Table S3 includes the results of previous studies. *P*-values in the omnibus test of model coefficients versus a model with intercept only were statistically significant ($P<0.05$) for all the models for each WCST score, and all the models fit the data adequately in the Hosmer and Lemeshow goodness of fit test.

DISCUSSION

This study is the first to investigate the relationships between WCST factor scores and clinical and socio-demographic factors in Japanese patients with schizophrenia by multiple logistic regression analysis. We showed the distribution of each WCST score (Figure 1). We conducted principal component analysis and identified two factors. The components of these two factors were similar to previous studies.[19-21] Thus, we could reduce the number of WCST outcomes from five indicators to two factors (Table 3). In assessment of cognitive function in patients with schizophrenia, using the WCST factor scores may reduce the possibility of type I errors due to multiple comparisons. We analyzed the relationship between these two factors and clinical and socio-demographic factors with multiple logistic regression analysis. We found that age, education years, PANSS negative scale score, and duration of illness affected the two WCST factor scores.

Principal component analysis

Our study showed that factor 1 mainly consisted of CA, PEM, PEN, and TE and factor 2 mainly consisted of DMS. In the previous studies with principal component analysis and factor analysis of WCST scores in patients with schizophrenia, Categories Complete (CC) (an indicator examining numbers of categories achieved in the same way as CA), PE (an indicator examining perseveration in the same way as PEM and PEN) and TE mainly constituted one factor. Failure to Maintain Set (FMS) (an indicator examining difficulty of maintaining set, similar to DMS) mainly constituted another factor.[19-21] Our

results resembled the results of the principal component analysis and factor analysis of WCST in these previous studies.[19-21]

Factor 1, which included representative indicators (CC, PE, etc.), was named as 'general executive functioning' in a previous study.[21] Therefore, factor 1 in our study also may represent general executive functioning. In our study, factor 1 score showed a high contribution ratio of the total variance (65.6%) in principal component analysis of WCST scores in patients with schizophrenia. WCST factor scores calculated by principal component analysis may be useful for reducing the possibility of type I errors due to multiple comparisons.

Factor 1 and factor 2 in our study resembled those in previous studies.[19-21] Therefore, the KWCST measures cognitive function similarly to the traditional WCST.

Main analysis

We identified clinical and socio-demographic factors (age, education years, and PANSS negative scale score) affecting WCST factor 1 score. We also identified a clinical and socio-demographic factor (duration of illness) affecting WCST factor 2 score. This is an important new finding. Comparing the three main previous studies [9 10 23] with the current study, we summarized shared and different findings, shown in Table 4.

The shared findings were that age and PANSS negative scale score were related to WCST scores (Table 4).[9 10 23]

Two findings differed from previous studies (Table 4).[9 10 23] First, we

found a new relationship between education years and WCST scores. Second, we found no relationship between age of onset and WCST scores. Differences in the results between previous studies [9 10 23] and our study may be explained by differences of ethnicity, distribution of age and education years, types of statistical analysis used, and the version of WCST. These differences suggest that future studies about WCST should be conducted with attention to these conditions.

CPZ equivalent doses did not affect the WCST scores in this study. This result was in the same direction as one meta-analysis (n=4524) though recent studies had suggested the possibility of an effect.[31 39 40] Future studies will be necessary to clarify whether CPZ equivalent doses affect WCST scores under other conditions.

PANSS positive scale score did not affect the WCST scores but the PANSS negative scale score did. A recent meta-analysis (n=6519) suggested that negative symptoms related to cognitive performance in patients with schizophrenia whereas positive symptoms did not.[41] This suggests that the relationships between PANSS positive and negative scale scores and WCST scores in this study may be reasonable.

Sub-analysis

We found that factor 1 score and factor 1 score's main components (CA, PEM, PEN and TE) related to age and education years (Table S4 (Web only file)).

The effect of duration of illness on WCST factor 2 score, which was mainly influenced by DMS, is the novel finding of the main analysis. However, DMS is not significantly associated with the duration of illness in the sub-analysis (Table S4 (Web only file)). This discrepancy between the main analysis and sub-analysis may be derived from the difference between DMS and factor 2 (Factor 2 included not only DMS, but also CA, PEM, PEN and TE).

Limitations

There are several limitations in this study. First, other clinical and socio-demographic factors that were not investigated in the current study could affect WCST scores. Candidates for such clinical and socio-demographic factors are IQ,[42] participants' dominant arm, experience with using a computer, doses of drugs affecting cognitive performance (anticholinergics, benzodiazepines, etc), sleep,[43] eating, and risk factors of arteriosclerosis (BMI, blood pressure, etc).[44] It may be useful to include these factors in future studies. Second, the WCST indicators (CA, PEM, PEN, TE and DMS scores) in our study did not cover all WCST indicators; we selected the major five indicators. We might find other factors by principal component analysis or new relationships between new WCST factors and clinical and socio-demographic factors if we included other clinical indicators. Third, we dichotomized continuous variables (WCST factor scores) in the multiple logistic regression analysis. Therefore, careful interpretation of the results may be needed, considering the statistical weak points of dichotomizing continuous variables.[45]

Conclusion

This study is the first study that investigated clinical and socio-demographic factors affecting WCST factor scores calculated by principal component analysis in patients with schizophrenia. The study was conducted in a relatively large Japanese population. We showed distribution of measured five WCST indicators in patients with schizophrenia and confirmed two WCST factors by principal component analysis. Age, education years, PANSS negative scale score and duration of illness affected WCST scores in patients with schizophrenia. The interaction between the duration of illness and a factor of the WCST needs further confirmation in future studies because there was a discrepancy between the results of the main analysis and the sub-analysis in this study.

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FOOTNOTES

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Competing interests

None

Ethics approval

This study was approved under the guidelines for epidemiological studies by the Nagoya University Graduate School of Medicine and Nagoya University Hospital Ethics Review Committee and was conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from each subject before the start of the study.

Contributors

MB, TKo and NO conceived and designed the experiments. MB, TKo, TKi, KK and YA performed the experiments. MB, TKo, BA, TO, NK, TI and NO analyzed the data. MB, TKo and YA contributed reagents/materials/analysis tools. MB, TKo, TO, BA and NO wrote the paper.

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Not commissioned; externally peer reviewed.

Data sharing statement

No additional data are available.

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FIGURE LEGENDS

Figure 1. Distribution of WCST scores in patients with schizophrenia (*n*=131)

None of the distribution was normal distribution.

Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set

[a]. Standard deviation

[b]. % of cases

Figure 2. Component plot in principal component analysis of WCST scores in patients with schizophrenia (*n*=131)

Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set

Table 1. Profiles of patients with schizophrenia

Table 2. Correlation coefficients for WCST scores in patients with schizophrenia

Table 3. Factor loadings in principal component analysis in patients with schizophrenia (*n*=131)

Table 4. Clinical and socio-demographic factors for WCST scores of patients with schizophrenia in the current study (main analysis) and for previous studies

APPENDICES

Table S1 (Web only file). Multiple logistic regression analysis of WCST factor scores in patients with schizophrenia (*n*=131)

Table S2 (Web only file). Multiple logistic regression analysis of WCST scores in patients with schizophrenia (*n*=131)

Table S3 (Web only file). Clinical and socio-demographic factors for WCST scores of patients with schizophrenia in this study (sub-analysis) and previous studies

Table S4 (Web only file). Clinical and socio-demographic factors for WCST scores of patients with schizophrenia in this study (main analysis and sub-analysis)

Information S1 (Web only file). Why we did not use multiple linear regression analysis in this study.

Information S2 (Web only file). Why we used the median as a cutoff point for dependent variables (WCST factor scores) in the multiple logistic regression analysis.

Table 1. Profiles of patients with schizophrenia

		Patients with schizophrenia (*n* =131)	
Sex		Male	Female
		84	47
		Average	(SD[a])
Age (y)		43.5	(13.8)
Education (y)		12.4	(2.4)
Age of onset (y)		26.3	(10.0)
Duration of illness (y)		17.0	(12.8)
Chlorpromazine equivalent doses (mg)		618.4	(391.1)
PANSS scale	Positive (7-49)	16.5	(5.3)
	Negative (7-49)	19.3	(5.6)
	General (16-112)	36.6	(9.4)
	Total (30-210)	72.4	(18.1)

[a]. Standard deviation

Table 2. Correlation coefficients for WCST scores in patients with schizophrenia

		Patients with schizophrenia (n=131)				
		CA	PEM	PEN	TE	DMS
correlation coefficient[a]	CA	-	-	-	-	-
	PEM	-0.70**	-	-	-	-
	PEN	-0.79**	0.73**	-	-	-
	TE	-0.88**	0.71**	0.89**	-	-
	DMS	-0.58**	0.30*	0.28*	0.30*	-

*: P<0.01, **: P<0.001

Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set

[a]. Spearman's rank correlation coefficient

Table 3. Factor loadings in principal component analysis in patients with schizophrenia (*n*=131)

		factor 1	factor 2
WCST score	CA	-0.89	0.36
	PEM	0.84	0.27
	PEN	0.92	0.27
	TE	0.93	0.13
	DMS	0.29	-0.93
Variance (%) explained by each factor		65.6	23.2
Cumulative explained variance (%)		65.6	88.9

Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set

Factor analysis was based on principal component method without rotation.

Two factors were retained using the eigenvalue >1 criterion.

Table 4. Clinical and socio-demographic factors for WCST scores of patients with schizophrenia in the current study (main analysis) and for previous studies

	Patients with schizophrenia (n =131) Main analysis		Previous studies		
	Factor 1 score	Factor 2 score	CA[a]	PE[a]	TE[a]
Sex			n/a	n/a	n/a
Age	***		n.s.[b]	○[b]	n/a
Education years	**		n.s.[b]	n.s.[b]	n/a
Age of onset			n.s.[c]	○[c]	n/a
Duration of illness		*	n.s.[b]	n.s.[b]	n/a
Chlorpromazine equivalent doses			n/a	n/a	n/a
PANSS score positive (7-49)			n.s.[d]	n/a	n/a
PANSS score negative (7-49)	*		○[d]	n/a	n/a
PANSS score general (16-112)			n.s.[d]	n/a	n/a
hit rate	0.77	0.58	n/a	n/a	n/a

*: P<0.05, **: P<0.01, ***: P<0.001

Abbreviations: CA, Categories Achieved; PE, Perseverative errors; TE, Total Errors; n/a, data not available; n.s., not significant

[a]. CA, PE and TE were included in factor 1 in a previous study.

[b]. Reference 10, [c]. Reference 23, [d]. Reference 9

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Wisconsin Card Sorting Test Scores and Clinical and Socio-demographic Correlates in Schizophrenia: Multiple Logistic Regression Analysis

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Wisconsin Card Sorting Test Scores and Clinical and Socio-demographic Correlates in Schizophrenia: Multiple Logistic Regression Analysis

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ABSTRACT

Objectives: This study investigated what clinical and socio-demographic factors affected Wisconsin Card Sorting Test (WCST) factor scores of patients with schizophrenia to evaluate parameters or items of the WCST.

Design: Cross-sectional study

Setting: Patients with schizophrenia from three hospitals participated.

Participants: Participants were recruited from July 2009 to August 2011. 131 Japanese patients with schizophrenia (84 males and 47 females, 43.5±13.8 years (mean ± SD)) entered and completed the study. Participants were recruited in the study if they 1) met DSM-IV criteria for schizophrenia; 2) were physically healthy; and 3) had no mood disorders, substance abuse, neurodevelopmental disorders, epilepsy, or mental retardation. We examined their basic clinical and socio-demographic factors (sex, age, education years, age of onset, duration of illness, chlorpromazine equivalent doses, and the Positive and Negative Syndrome Scale [PANSS] scores).

Interventions: -

Primary and secondary outcome measures: All patients carried out the WCST Keio version. Five indicators were calculated, including Categories Achieved (CA), Perseverative Errors in Milner (PEM) and Nelson (PEN), Total Errors (TE), and Difficulties of Maintaining Set (DMS). From the principal component analysis, we identified two factors (1 and 2). We assessed the relationship between these factor scores and clinical and socio-demographic

factors, using multiple logistic regression analysis.

Results: Factor 1 was mainly composed of CA, PEM, PEN, and TE. Factor 2 was mainly composed of DMS. The factor 1 score was affected by age, education years, and the PANSS negative scale score. The factor 2 score was affected by duration of illness.

Conclusions: Age, education years, PANSS negative scale score and duration of illness affected WCST factor scores in patients with schizophrenia. Using WCST factor scores may reduce the possibility of type I errors due to multiple comparisons.

Trial registration: -

ARTICLE SUMMARY

Article focus

- To investigate relationships between Wisconsin Card Sorting Test (WCST) factor scores and clinical and socio-demographic factors in Japanese patients with schizophrenia using multiple logistic regression analysis
- To show distribution of each WCST score for patients with schizophrenia

Key messages

- Age, education years, Positive and Negative Syndrome Scale (PANSS) negative scale score, and duration of illness affected two WCST factor scores.
- Using WCST factor scores may reduce the possibility of type I errors due to multiple comparisons.

Strengths and limitations of this study

- We conducted principal component analysis and identified two WCST factors. Components of two WCST factors in this study were similar to previous studies.
- This is the first study to investigate relationships between WCST factor scores and clinical and socio-demographic factors in patients with schizophrenia.
- We identified a clinical and socio-demographic factor (duration of illness) that affected the WCST factor 2 score. This is a new finding.

INTRODUCTION

Cognitive impairment in patients with schizophrenia has been evaluated as an indicator of outcome regarding social functioning and quality of life.[1 2] It is reported that cognitive performance in patients with schizophrenia declines from prodrome to onset of schizophrenia (first episode).[3] Moreover, it is reported that decline of cognitive performance exists before onset of schizophrenia.[3] Many studies using brain imaging suggest that neurobiological changes in the brain are related to the cognitive impairment in schizophrenia.[4-6] Therefore, some researchers regard cognitive impairment, rather than positive and negative symptoms, as the core pathology of schizophrenia.[7]

However, there are several problems when analyzing cognitive impairment in schizophrenia. First, positive and negative syndromes modify cognitive performance.[8 9] Second, intelligence level, intelligence profile (verbal IQ and performance IQ), and educational level could affect cognitive impairment in patients with schizophrenia.[10-12] In brief, many factors have the potential to affect cognitive impairment in patients with schizophrenia. It is necessary to clarify the relationship between cognitive performance in patients with schizophrenia and clinical and socio-demographic factors in order to investigate what factors affect cognitive impairment in patients with schizophrenia.

Many neurocognitive tests have been used in order to evaluate cognitive performance in schizophrenia. The Wisconsin Card Sorting Test (WCST) is a neurocognitive test using cards and is one of the most frequently used executive

function measures.[13] A functional brain imaging study showed widespread activation across frontal and non-frontal brain regions during WCST performance.[14] It has been reported that each WCST score was related with social functioning in patients with schizophrenia.[15-17]

Recent reports suggest that WCST performance may decline during disease progression from prodrome to onset of schizophrenia. A steady (nonsignificant) progression of impairment on WCST Perseverative Errors (PE) was demonstrated from basic symptom at-risk (BS), ultra high-risk (UHR), and first-episode (FE) groups (BS: z=−0.74; UHR: z=−0.88; FE: z=−0.97).[3] However, negative and depressive symptoms may modify WCST performance in patients with schizophrenia,[9 18] and many other factors (for example, premorbid IQ) may modify WCST scores.[11]

Factor structures of WCST in patients with schizophrenia have been investigated using principal component analysis and factor analysis of WCST scores.[19-21] Differences in cognitive performance of WCST scores (Categories Achieved (CA) and PE) were shown between patients with schizophrenia and healthy controls (Cohens' d=0.91 and 0.53) in one meta-analysis, but age, education years, and other clinical and socio-demographic factors were not matched in the statistical analysis.[10] In another previous study, age and education years affected CA and PE scores.[22] In a different study, age affected PE score but education years did not affect either CA or PE scores.[10] Additional two studies showed age of onset affected PE score [23] and the Positive and Negative Syndrome Scale (PANSS) negative scale score affected CA score in patients with schizophrenia.[9] These findings

indicate that it is important to consider all clinical and socio-demographic factors to clarify which affect WCST scores in patients with schizophrenia.

In previous studies, the Wechsler Adult Intelligence Scale (WAIS) Full Scale IQ (FSIQ) showed significant correlations (P<0.05) with CA, Perseverative Errors in Milner (PEM), and Nelson (PEN) and TE scores, while items 3 and 16 of the Brief Psychiatric Rating Scale (BPRS) showed significant correlations (P<0.05) with CA, PEN and TE scores.[24] Affective flattening & blunting and avolition-apathy on the Scale for the Assessment of Negative Symptoms (SANS) showed significant correlations (P<0.05) with CA, PEM, PEN, TE and Difficulties of Maintaining Set (DMS) scores of Wisconsin Card Sorting Test Keio version (KWCST) in Japanese patients with schizophrenia (n=33).[24] However, there is no previous study that investigated other clinical and socio-demographic factors (except IQ and negative symptoms) affecting KWCST scores. Therefore, we investigated clinical and socio-demographic factors affecting scores of KWCST [25] (Japanese computerized version [26]) in Japanese patients with schizophrenia.

METHODS AND PROCEDURES

Participants

The study included 131 unrelated Japanese patients with schizophrenia (age 43.5±13.8 (mean ± SD), 84 males and 47 females) from three hospitals. The recruitment took place from both the outpatient department and the acute /

chronic wards in three hospitals. 51 outpatients (15 acute phase patients and 36 chronic phase patients) and 55 inpatients (37 acute phase patients and 18 chronic phase patients) were recruited. 25 patients were unspecified (outpatients or inpatients: 20 acute phase patients and 5 chronic phase patients). Participants were recruited from July 2009 to August 2011. Profiles of all the patients are shown in Table 1. 104 patients (78%) were receiving concomitant medications, which could include benzodiazepines, barbiturates, anticholinergics, mood stabilizers, and antidepressants.

This study protocol was approved by Nagoya University Graduate School of Medicine and Nagoya University Hospital Ethics Review Committee, and written informed consent was obtained from each participant. Participants were recruited for the study if they 1) met DSM-IV criteria for schizophrenia; 2) were physically healthy; and 3) had no mood disorders, substance abuse, neurodevelopmental disorders, epilepsy, or mental retardation. Consensus diagnoses were made by at least two experienced psychiatrists according to DSM-IV criteria on the basis of unstructured interviews with patients with schizophrenia (or their family members) and review of patients' medical records. Less than 5% of participants were excluded due to a lack of consensus. All subjects were unrelated to each other and lived in the central area of the mainland of Japan. A general characterization and psychiatric assessment of the subjects is available elsewhere.[27-29]

Measurement Settings

The WCST mainly assesses executive function, including cognitive

flexibility in response to feedback.[30] KWCST is the Japanese version of the WCST modified by Kashima.[25] KWCST consists of a card version and a computerized version, both of which have been used to investigate cognitive performance in patients with schizophrenia.[31 32] In KWCST, there are two levels of instruction.[33] The subject is told that, at the first level, this is a test of classification based on any of the three categories of color, shape, or number, and that, at the second level, the tester's categories change when the subject continues to get correct answers at fixed times. The computerized version uses instruction through letters on the monitor and the synthetic sound of the computer in order to prevent potential bias derived from a confrontation test. We selected specific indicators (CA, PEM, PEN, TE and DMS) of KWCST in this analysis, given that these indicators were investigated in previous studies.[31 32] The computerized program investigates these indicators at the second level only if the CA score at the first level is equal or less than 3. We got data for the following five indicators [32 34] at the first and second levels in this study.

(1) CA: the number of categories for which six consecutive correct responses are achieved (maximum CA is 8).

(2) PEM: the number of incorrect responses in the same category as the immediately preceding correct response after the tester's categories change (maximum PEM is 47).

(3) PEN: the number of incorrect responses in the same category as the immediately preceding incorrect response (maximum PEN is 47).

(4) TE: the total number of incorrect responses (maximum TE is 48).

(5) DMS: the number of times an incorrect response occurs after 2 to 5

consecutive correct responses (maximum DMS is 16).

We analyzed KWCST (Japanese computerized version [26]) (Shimane University, Shimane, Japan) scores at the first level of the patients with schizophrenia. Psychiatrists in three hospitals performed the KWCST assessment.

Clinical and socio-demographic factors

We investigated sex, age, education years, age of onset, duration of illness, chlorpromazine equivalent doses, and PANSS scores as clinical and socio-demographic factors. Age was calculated based on the day we evaluated KWCST scores. Education years were calculated from elementary school entrance to the graduation or dropout of the last institution of higher education, which consisted of junior high school, senior high school, vocational school, junior college, university and graduate school. Age of onset was the age at onset of schizophrenia in each patient and was based on review of medical records. Duration of illness was defined from age of onset to age at the time of study. Chlorpromazine (CPZ) equivalent doses were the identified dose ratios of each antipsychotic in relation to 100 mg of chlorpromazine.[35] CPZ equivalent doses in this study were calculated based on the method by Inagaki and Inada.[36 37] PANSS is a standardized scale for evaluating positive and negative symptoms of schizophrenia and was used to evaluate severity of schizophrenia in the patients.[38]

Statistical analysis

Clinical profiles of the patients with schizophrenia are shown in Table 1. We investigated correlations of the five indicators of the KWCST (CA, PEM, PEN, TE and DMS) in patients with schizophrenia by Spearman's Rank Correlation Test.

Principal component analysis

The principal component model was based on Pearson's correlation matrix. We showed the Pearson's product moment correlation coefficients between the five indicators of WCST in Table S1 (Web only file). WCST factors were identified by principal component analysis of the five indicators without rotation. Factors were retained using the eigenvalue >1 criterion.

Main analysis

In the main analysis, we investigated what clinical and socio-demographic factors affected WCST factor scores in a multiple logistic regression analysis. Our reasoning for not using multiple linear regression is explained in Information S1 (Web only file). The dependent variables were WCST factor scores and independent variables were the following candidate clinical and socio-demographic factors: sex, age, education years, age of onset, duration of illness, CPZ equivalent doses, and PANSS (positive, negative and general psychopathology scale) scores. We made a dummy conversion variable (1 or 0) for sex. We converted factor scores into categorical variables (1 or 0), using cutoff values that were median values of the factor scores. The median was chosen as a cutoff point for dependent variables based on reasons

explained in Information S2 (Web only file). In our multiple logistic regression analysis, we did additional two tests. First, we did an omnibus test of model coefficients versus a model with intercept only. This test detects whether a model is significant (P<0.05) or not; this is a test of the null hypothesis that adding any variables to the model has not significantly increased our ability to predict the dependent variable. A model is useless if the P-value in omnibus test was >0.05. Second, we did a Hosmer and Lemeshow goodness of fit test, which shows how well the model fits the data with P>0.05 indicating good fit; this is a test of the null hypothesis that there is a linear relationship between the predictor variables and the log odds of the criterion variable. The hit rate in multiple logistic regression analysis is a measure how well a model predicts the dependent variable.

Sub-analysis

In the sub-analysis, we also investigated what clinical and socio-demographic factors affected the five indicators of WCST in the multiple logistic regression analysis. We used multiple logistic regression analysis in the sub-analysis in order to compare the results between main and sub-analysis. In this analysis, the dependent variables were the five indicators of WCST and independent variables were the candidate clinical and socio-demographic factors. We compared the results of the multiple logistic regression analysis with the results of previous studies.[9 10 23]

Software

IBM SPSS statistical software (IBM Japan, Tokyo, Japan), version 19 was used for analyses. The significance level was set at *P*=0.05 using a two-tailed t-test.

RESULTS

Distribution of the WCST (CA, PEM, PEN, TE and DMS) scores in patients with schizophrenia is shown in Figure 1. The numbers of patients in the following analyses were CA *n*=131, PEM *n*=122, PEN *n*=131, TE *n*=115 and DMS *n*=131 because of missing values in the data.

Spearman's rank correlation coefficients between the five indicators of WCST are shown in Table 2. Although no strong correlation (>0.8) was observed in any of these clinical and socio-demographic factors, the Spearman's correlation between PANSS negative scale score and PANSS general psychopathology scale score was high (0.74).

Principal component analysis

Two factors (1 and 2) were identified in principal component analysis of the five indicators of WCST. Factor 1 mainly consisted of CA, PEM, PEN, and TE, and accounted for 65.6% of the total variance. Factor 2 mainly consisted of DMS and accounted for 23.2% of the total variance (Table 3 and Figure 2). We converted the factor 1 and factor 2 scores into categorical variables (1 or 0) using cutoff values. The cutoff values were the median values (factor 1: -0.299; factor 2: 0.080). We used these categorical variables as dependent variables in multiple logistic regression analysis.

Main analysis

Age, education years, and PANSS negative scale score significantly affected factor 1 score, and the duration of illness significantly affected factor 2 score in patients with schizophrenia (Table 4). The details of the results from the multiple logistic regression analyses are shown in Table S2 (Web only file). *P*-values in an omnibus test of model coefficients versus a model with intercept only were statistically significant ($P<0.05$) for all the models in WCST factor scores. In the Hosmer and Lemeshow goodness of fit test, all the models fit the data adequately with $P>0.05$. Factor 1 score may be predicted precisely by this model considering hit rate (0.77).

CPZ equivalent doses did not affect the WCST scores. PANSS positive scale score did not affect the WCST scores; whereas PANSS negative scale score did.

Sub-analysis

In the sub-analyses, age, education years, and PANSS negative scale score significantly affected CA score. Age and education years significantly affected PEM, PEN, and TE scores, and age significantly affected DMS score in patients with schizophrenia. The details of these results are shown in Table S3 and Table S4 (Web only file); Table S4 includes the results of previous studies. *P*-values in the omnibus test of model coefficients versus a model with intercept only were statistically significant ($P<0.05$) for all the models for each WCST score, and all the models fit the data adequately in the Hosmer and Lemeshow

goodness of fit test.

DISCUSSION

This study is the first to investigate the relationships between WCST factor scores and clinical and socio-demographic factors in Japanese patients with schizophrenia by multiple logistic regression analysis. We showed the distribution of each WCST score (Figure 1). We conducted principal component analysis and identified two factors. The components of these two factors were similar to previous studies.[19-21] Thus, we could reduce the number of WCST outcomes from five indicators to two factors (Table 3). In assessment of cognitive function in patients with schizophrenia, using the WCST factor scores may reduce the possibility of type I errors due to multiple comparisons. We analyzed the relationship between these two factors and clinical and socio-demographic factors with multiple logistic regression analysis. We found that age, education years, PANSS negative scale score, and duration of illness affected the two WCST factor scores.

Principal component analysis

Our study showed that factor 1 mainly consisted of CA, PEM, PEN, and TE and factor 2 mainly consisted of DMS. In the previous studies with principal component analysis and factor analysis of WCST scores in patients with schizophrenia, Categories Complete (CC) (an indicator examining numbers of categories achieved in the same way as CA), PE (an indicator examining perseveration in the same way as PEM and PEN) and TE mainly constituted one

factor. Failure to Maintain Set (FMS) (an indicator examining difficulty of maintaining set, similar to DMS) mainly constituted another factor.[19-21] Our results resembled the results of the principal component analysis and factor analysis of WCST in these previous studies.[19-21]

Factor 1, which included representative indicators (CC, PE, etc.), was named as 'general executive functioning' in a previous study.[21] Therefore, factor 1 in our study also may represent general executive functioning. In our study, factor 1 score showed a high contribution ratio of the total variance (65.6%) in principal component analysis of WCST scores in patients with schizophrenia. WCST factor scores calculated by principal component analysis may be useful for reducing the possibility of type I errors due to multiple comparisons. Factor 1 and factor 2 in our study resembled those in previous studies.[19-21] Therefore, the KWCST measures cognitive function similarly to the traditional WCST.

We compared the Spearman's rank correlation coefficients with the Pearson's product moment correlation coefficients between the five indicators of WCST (Table 2 and Table S1). Correlations between CA, PEM, PEN and TE and a correlation between CA and DMS were statistically significant (P<0.001). In this point, both correlation coefficients showed the same direction. Therefore, using Pearson's correlation matrix, instead of Spearman's correlation matrix, in principal component analysis may be justified in our study.

Main analysis

We identified clinical and socio-demographic factors (age, education

years, and PANSS negative scale score) affecting WCST factor 1 score. We also identified a clinical and socio-demographic factor (duration of illness) affecting WCST factor 2 score. This is an important new finding. Comparing the three main previous studies [9 10 23] with the current study, we summarized shared and different findings, shown in Table 4.

The shared findings were that age and PANSS negative scale score were related to WCST scores (Table 4).[9 10 23]

Two findings differed from previous studies (Table 4).[9 10 23] First, we found a new relationship between education years and WCST scores. Second, we found no relationship between age of onset and WCST scores. Differences in the results between previous studies [9 10 23] and our study may be explained by differences of ethnicity, distribution of age and education years, types of statistical analysis used, and the version of WCST. These differences suggest that future studies about WCST should be conducted with attention to these conditions.

CPZ equivalent doses did not affect the WCST scores in this study. This result was in the same direction as one meta-analysis (n=4524) though recent studies had suggested the possibility of an effect.[31 39 40] Future studies will be necessary to clarify whether CPZ equivalent doses affect WCST scores under other conditions.

PANSS positive scale score did not affect the WCST scores but the PANSS negative scale score did. A recent meta-analysis (n=6519) suggested that negative symptoms related to cognitive performance in patients with schizophrenia whereas positive symptoms did not.[41] This suggests that the

relationships between PANSS positive and negative scale scores and WCST scores in this study may be reasonable.

Sub-analysis

We found that factor 1 score and factor 1 score's main components (CA, PEM, PEN and TE) related to age and education years (Table S5 (Web only file)).

The effect of duration of illness on WCST factor 2 score, which was mainly influenced by DMS, is the novel finding of the main analysis. However, DMS is not significantly associated with the duration of illness in the sub-analysis (Table S5 (Web only file)). This discrepancy between the main analysis and sub-analysis may be derived from the difference between DMS and factor 2 (Factor 2 included not only DMS, but also CA, PEM, PEN and TE).

Limitations

There are several limitations in this study. First, other clinical and socio-demographic factors that were not investigated in the current study could affect WCST scores. Candidates for such clinical and socio-demographic factors are IQ,[42] participants' dominant arm, experience with using a computer, doses of drugs affecting cognitive performance (anticholinergics, benzodiazepines, etc), sleep,[43] eating, and risk factors of arteriosclerosis (BMI, blood pressure, etc).[44] It may be useful to include these factors in future studies. Second, the

WCST indicators (CA, PEM, PEN, TE and DMS scores) in our study did not cover all WCST indicators; we selected the major five indicators. We might find other factors by principal component analysis or new relationships between new WCST factors and clinical and socio-demographic factors if we included other clinical indicators. Third, instead of using Spearman's correlation matrix in the principal component analysis, which might be more appropriate method in terms of the non-normal distribution of five WCST indicators, we used Pearson's correlation matrix. Fourth, we dichotomized continuous variables (WCST factor scores) in the multiple logistic regression analysis. Therefore, careful interpretation of the results may be needed, considering the statistical weak points.[45]

Conclusion

This study is the first study that investigated clinical and socio-demographic factors affecting WCST factor scores calculated by principal component analysis in patients with schizophrenia. The study was conducted in a relatively large Japanese population. We showed distribution of measured five WCST indicators in patients with schizophrenia and confirmed two WCST factors by principal component analysis. Age, education years, PANSS negative scale score and duration of illness affected WCST scores in patients with schizophrenia. The interaction between the duration of illness and a factor of the WCST needs further confirmation in future studies because there was a discrepancy between the results of the main analysis and the sub-analysis in this study.

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FOOTNOTES

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Competing interests

None

Ethics approval

This study was approved under the guidelines for epidemiological studies by the Nagoya University Graduate School of Medicine and Nagoya University Hospital Ethics Review Committee and was conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from each subject before the start of the study.

Contributors

MB, TKo and NO conceived and designed the experiments. MB, TKo, TKi, KK and YA performed the experiments. MB, TKo, BA, TO, NK, TI and NO analyzed the data. MB, TKo and YA contributed reagents/materials/analysis tools. MB, TKo, TO, BA and NO wrote the paper.

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Data sharing statement

No additional data are available.

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FIGURE LEGENDS

Figure 1. Distribution of WCST scores in patients with schizophrenia (*n*=131)

None of the distribution was normal distribution.

Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set

[a]. Standard deviation

[b]. % of cases

Figure 2. Component plot in principal component analysis of WCST scores in patients with schizophrenia (*n*=131)

Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set

Table 1. Profiles of patients with schizophrenia

Table 2. Correlation coefficients for WCST scores in patients with schizophrenia

Table 3. Factor loadings in principal component analysis in patients with schizophrenia (*n*=131)

Table 4. Clinical and socio-demographic factors for WCST scores of patients with schizophrenia in the current study (main analysis) and for previous studies

APPENDICES

Table S1 (Web only file). Pearson's product moment correlation coefficients for WCST scores in patients with schizophrenia

Table S2 (Web only file). Multiple logistic regression analysis of WCST factor scores in patients with schizophrenia (*n*=131)

Table S3 (Web only file). Multiple logistic regression analysis of WCST scores in patients with schizophrenia (*n*=131)

Table S4 (Web only file). Clinical and socio-demographic factors for WCST scores of patients with schizophrenia in this study (sub-analysis) and previous studies

Table S5 (Web only file). Clinical and socio-demographic factors for WCST scores of patients with schizophrenia in this study (main analysis and sub-analysis)

Information S1 (Web only file). Why we did not use multiple linear regression analysis in this study.

Information S2 (Web only file). Why we used the median as a cutoff point for dependent variables (WCST factor scores) in the multiple logistic regression analysis.

Table 1. Profiles of patients with schizophrenia

		Patients with schizophrenia (*n* =131)	
Sex		Male	Female
		84	47
		Average	(SD[a])
Age (y)		43.5	(13.8)
Education (y)		12.4	(2.4)
Age of onset (y)		26.3	(10.0)
Duration of illness (y)		17.0	(12.8)
Chlorpromazine equivalent doses (mg)		618.4	(391.1)
PANSS scale	Positive (7-49)	16.5	(5.3)
	Negative (7-49)	19.3	(5.6)
	General (16-112)	36.6	(9.4)
	Total (30-210)	72.4	(18.1)

[a]. Standard deviation

Table 2. Correlation coefficients for WCST scores in patients with schizophrenia

		Patients with schizophrenia (n=131)				
		CA	PEM	PEN	TE	DMS
correlation coefficient[a]	CA	-	-	-	-	-
	PEM	-0.70**	-	-	-	-
	PEN	-0.79**	0.73**	-	-	-
	TE	-0.88**	0.71**	0.89**	-	-
	DMS	-0.58**	0.30*	0.28*	0.30*	-

*: P<0.01, **: P<0.001

Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set

[a]. Spearman's rank correlation coefficient

Table 3. Factor loadings in principal component analysis in patients with schizophrenia (*n*=131)

		factor 1	factor 2
WCST score	CA	-0.89	0.36
	PEM	0.84	0.27
	PEN	0.92	0.27
	TE	0.93	0.13
	DMS	0.29	-0.93
Variance (%) explained by each factor		65.6	23.2
Cumulative explained variance (%)		65.6	88.9

Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set

Factor analysis was based on principal component method without rotation.

Two factors were retained using the eigenvalue >1 criterion.

Table 4. Clinical and socio-demographic factors for WCST scores of patients with schizophrenia in the current study (main analysis) and for previous studies

	Patients with schizophrenia (*n* =131) Main analysis		Previous studies		
	Factor 1 score	Factor 2 score	CA[a]	PE[a]	TE[a]
Sex			n/a	n/a	n/a
Age	***		n.s.[b]	○[b]	n/a
Education years	**		n.s.[b]	n.s.[b]	n/a
Age of onset			n.s.[c]	○[c]	n/a
Duration of illness		*	n.s.[b]	n.s.[b]	n/a
Chlorpromazine equivalent doses			n/a	n/a	n/a
PANSS score positive (7-49)			n.s.[d]	n/a	n/a
PANSS score negative (7-49)	*		○[d]	n/a	n/a
PANSS score general (16-112)			n.s.[d]	n/a	n/a
hit rate	0.77	0.58	n/a	n/a	n/a

*: *P*<0.05, **: *P*<0.01, ***: *P*<0.001

Abbreviations: CA, Categories Achieved; PE, Perseverative errors; TE, Total Errors; n/a, data not available; n.s., not significant

[a]. CA, PE and TE were included in factor 1 in a previous study.

[b]. Reference 10, [c]. Reference 23, [d]. Reference 9

Wisconsin Card Sorting Test Scores and Clinical and Socio-demographic Correlates in Schizophrenia: Multiple Logistic Regression Analysis

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ABSTRACT

Objectives: This study investigated what clinical and socio-demographic factors affected Wisconsin Card Sorting Test (WCST) factor scores of patients with schizophrenia to evaluate parameters or items of the WCST.

Design: Cross-sectional study

Setting: Patients with schizophrenia from three hospitals participated.

Participants: Participants were recruited from July 2009 to August 2011. 131 Japanese patients with schizophrenia (84 males and 47 females, 43.5±13.8 years (mean ± SD)) entered and completed the study. Participants were recruited in the study if they 1) met DSM-IV criteria for schizophrenia; 2) were physically healthy; and 3) had no mood disorders, substance abuse, neurodevelopmental disorders, epilepsy, or mental retardation. We examined their basic clinical and socio-demographic factors (sex, age, education years, age of onset, duration of illness, chlorpromazine equivalent doses, and the Positive and Negative Syndrome Scale [PANSS] scores).

Interventions: -

Primary and secondary outcome measures: All patients carried out the WCST Keio version. Five indicators were calculated, including Categories Achieved (CA), Perseverative Errors in Milner (PEM) and Nelson (PEN), Total Errors (TE), and Difficulties of Maintaining Set (DMS). From the principal component analysis, we identified two factors (1 and 2). We assessed the relationship between these factor scores and clinical and socio-demographic

factors, using multiple logistic regression analysis.

Results: Factor 1 was mainly composed of CA, PEM, PEN, and TE. Factor 2 was mainly composed of DMS. The factor 1 score was affected by age, education years, and the PANSS negative scale score. The factor 2 score was affected by duration of illness.

Conclusions: Age, education years, PANSS negative scale score and duration of illness affected WCST factor scores in patients with schizophrenia. Using WCST factor scores may reduce the possibility of type I errors due to multiple comparisons.

Trial registration: -

ARTICLE SUMMARY

Article focus

- To investigate relationships between Wisconsin Card Sorting Test (WCST) factor scores and clinical and socio-demographic factors in Japanese patients with schizophrenia using multiple logistic regression analysis
- To show distribution of each WCST score for patients with schizophrenia

Key messages

- Age, education years, Positive and Negative Syndrome Scale (PANSS) negative scale score, and duration of illness affected two WCST factor scores.
- Using WCST factor scores may reduce the possibility of type I errors due to multiple comparisons.

Strengths and limitations of this study

- We conducted principal component analysis and identified two WCST factors. Components of two WCST factors in this study were similar to previous studies.
- This is the first study to investigate relationships between WCST factor scores and clinical and socio-demographic factors in patients with schizophrenia.
- We identified a clinical and socio-demographic factor (duration of illness) that affected the WCST factor 2 score. This is a new finding.

INTRODUCTION

Cognitive impairment in patients with schizophrenia has been evaluated as an indicator of outcome regarding social functioning and quality of life.[1 2] It is reported that cognitive performance in patients with schizophrenia declines from prodrome to onset of schizophrenia (first episode).[3] Moreover, it is reported that decline of cognitive performance exists before onset of schizophrenia.[3] Many studies using brain imaging suggest that neurobiological changes in the brain are related to the cognitive impairment in schizophrenia.[4-6] Therefore, some researchers regard cognitive impairment, rather than positive and negative symptoms, as the core pathology of schizophrenia.[7]

However, there are several problems when analyzing cognitive impairment in schizophrenia. First, positive and negative syndromes modify cognitive performance.[8 9] Second, intelligence level, intelligence profile (verbal IQ and performance IQ), and educational level could affect cognitive impairment in patients with schizophrenia.[10-12] In brief, many factors have the potential to affect cognitive impairment in patients with schizophrenia. It is necessary to clarify the relationship between cognitive performance in patients with schizophrenia and clinical and socio-demographic factors in order to investigate what factors affect cognitive impairment in patients with schizophrenia.

Many neurocognitive tests have been used in order to evaluate cognitive performance in schizophrenia. The Wisconsin Card Sorting Test (WCST) is a neurocognitive test using cards and is one of the most frequently used executive

function measures.[13] A functional brain imaging study showed widespread activation across frontal and non-frontal brain regions during WCST performance.[14] It has been reported that each WCST score was related with social functioning in patients with schizophrenia.[15-17]

Recent reports suggest that WCST performance may decline during disease progression from prodrome to onset of schizophrenia. A steady (nonsignificant) progression of impairment on WCST Perseverative Errors (PE) was demonstrated from basic symptom at-risk (BS), ultra high-risk (UHR), and first-episode (FE) groups (BS: z=–0.74; UHR: z=–0.88; FE: z=–0.97).[3] However, negative and depressive symptoms may modify WCST performance in patients with schizophrenia,[9 18] and many other factors (for example, premorbid IQ) may modify WCST scores.[11]

Factor structures of WCST in patients with schizophrenia have been investigated using principal component analysis and factor analysis of WCST scores.[19-21] Differences in cognitive performance of WCST scores (Categories Achieved (CA) and PE) were shown between patients with schizophrenia and healthy controls (Cohens' d=0.91 and 0.53) in one meta-analysis, but age, education years, and other clinical and socio-demographic factors were not matched in the statistical analysis.[10] In another previous study, age and education years affected CA and PE scores.[22] In a different study, age affected PE score but education years did not affect either CA or PE scores.[10] Additional two studies showed age of onset affected PE score [23] and the Positive and Negative Syndrome Scale (PANSS) negative scale score affected CA score in patients with schizophrenia.[9] These findings

indicate that it is important to consider all clinical and socio-demographic factors to clarify which affect WCST scores in patients with schizophrenia.

In previous studies, the Wechsler Adult Intelligence Scale (WAIS) Full Scale IQ (FSIQ) showed significant correlations (P<0.05) with CA, Perseverative Errors in Milner (PEM), and Nelson (PEN) and TE scores, while items 3 and 16 of the Brief Psychiatric Rating Scale (BPRS) showed significant correlations (P<0.05) with CA, PEN and TE scores.[24] Affective flattening & blunting and avolition-apathy on the Scale for the Assessment of Negative Symptoms (SANS) showed significant correlations (P<0.05) with CA, PEM, PEN, TE and Difficulties of Maintaining Set (DMS) scores of Wisconsin Card Sorting Test Keio version (KWCST) in Japanese patients with schizophrenia (n=33).[24] However, there is no previous study that investigated other clinical and socio-demographic factors (except IQ and negative symptoms) affecting KWCST scores. Therefore, we investigated clinical and socio-demographic factors affecting scores of KWCST [25] (Japanese computerized version [26]) in Japanese patients with schizophrenia.

METHODS AND PROCEDURES

Participants

The study included 131 unrelated Japanese patients with schizophrenia (age 43.5±13.8 (mean ± SD), 84 males and 47 females) from three hospitals. The recruitment took place from both the outpatient department and the acute /

chronic wards in three hospitals. 51 outpatients (15 acute phase patients and 36 chronic phase patients) and 55 inpatients (37 acute phase patients and 18 chronic phase patients) were recruited. 25 patients were unspecified (outpatients or inpatients: 20 acute phase patients and 5 chronic phase patients). Participants were recruited from July 2009 to August 2011. Profiles of all the patients are shown in Table 1. 104 patients (78%) were receiving concomitant medications, which could include benzodiazepines, barbiturates, anticholinergics, mood stabilizers, and antidepressants.

This study protocol was approved by Nagoya University Graduate School of Medicine and Nagoya University Hospital Ethics Review Committee, and written informed consent was obtained from each participant. Participants were recruited for the study if they 1) met DSM-IV criteria for schizophrenia; 2) were physically healthy; and 3) had no mood disorders, substance abuse, neurodevelopmental disorders, epilepsy, or mental retardation. Consensus diagnoses were made by at least two experienced psychiatrists according to DSM-IV criteria on the basis of unstructured interviews with patients with schizophrenia (or their family members) and review of patients' medical records. Less than 5% of participants were excluded due to a lack of consensus. All subjects were unrelated to each other and lived in the central area of the mainland of Japan. A general characterization and psychiatric assessment of the subjects is available elsewhere.[27-29]

Measurement Settings

The WCST mainly assesses executive function, including cognitive

flexibility in response to feedback.[30] KWCST is the Japanese version of the WCST modified by Kashima.[25] KWCST consists of a card version and a computerized version, both of which have been used to investigate cognitive performance in patients with schizophrenia.[31 32] In KWCST, there are two levels of instruction.[33] The subject is told that, at the first level, this is a test of classification based on any of the three categories of color, shape, or number, and that, at the second level, the tester's categories change when the subject continues to get correct answers at fixed times. The computerized version uses instruction through letters on the monitor and the synthetic sound of the computer in order to prevent potential bias derived from a confrontation test. We selected specific indicators (CA, PEM, PEN, TE and DMS) of KWCST in this analysis, given that these indicators were investigated in previous studies.[31 32] The computerized program investigates these indicators at the second level only if the CA score at the first level is equal or less than 3. We got data for the following five indicators [32 34] at the first and second levels in this study.

(1) CA: the number of categories for which six consecutive correct responses are achieved (maximum CA is 8).

(2) PEM: the number of incorrect responses in the same category as the immediately preceding correct response after the tester's categories change (maximum PEM is 47).

(3) PEN: the number of incorrect responses in the same category as the immediately preceding incorrect response (maximum PEN is 47).

(4) TE: the total number of incorrect responses (maximum TE is 48).

(5) DMS: the number of times an incorrect response occurs after 2 to 5

consecutive correct responses (maximum DMS is 16).

We analyzed KWCST (Japanese computerized version [26]) (Shimane University, Shimane, Japan) scores at the first level of the patients with schizophrenia. Psychiatrists in three hospitals performed the KWCST assessment.

Clinical and socio-demographic factors

We investigated sex, age, education years, age of onset, duration of illness, chlorpromazine equivalent doses, and PANSS scores as clinical and socio-demographic factors. Age was calculated based on the day we evaluated KWCST scores. Education years were calculated from elementary school entrance to the graduation or dropout of the last institution of higher education, which consisted of junior high school, senior high school, vocational school, junior college, university and graduate school. Age of onset was the age at onset of schizophrenia in each patient and was based on review of medical records. Duration of illness was defined from age of onset to age at the time of study. Chlorpromazine (CPZ) equivalent doses were the identified dose ratios of each antipsychotic in relation to 100 mg of chlorpromazine.[35] CPZ equivalent doses in this study were calculated based on the method by Inagaki and Inada.[36 37] PANSS is a standardized scale for evaluating positive and negative symptoms of schizophrenia and was used to evaluate severity of schizophrenia in the patients.[38]

Statistical analysis

Clinical profiles of the patients with schizophrenia are shown in Table 1. We investigated correlations of the five indicators of the KWCST (CA, PEM, PEN, TE and DMS) in patients with schizophrenia by Spearman's Rank Correlation Test.

Principal component analysis

The principal component model was based on Pearson's correlation matrix. We showed the Pearson's product moment correlation coefficients between the five indicators of WCST in Table S1 (Web only file). WCST factors were identified by principal component analysis of the five indicators without rotation. Factors were retained using the eigenvalue >1 criterion.

Main analysis

In the main analysis, we investigated what clinical and socio-demographic factors affected WCST factor scores in a multiple logistic regression analysis. Our reasoning for not using multiple linear regression is explained in Information S1 (Web only file). The dependent variables were WCST factor scores and independent variables were the following candidate clinical and socio-demographic factors: sex, age, education years, age of onset, duration of illness, CPZ equivalent doses, and PANSS (positive, negative and general psychopathology scale) scores. We made a dummy conversion variable (1 or 0) for sex. We converted factor scores into categorical variables (1 or 0), using cutoff values that were median values of the factor scores. The median was chosen as a cutoff point for dependent variables based on reasons

explained in Information S2 (Web only file). In our multiple logistic regression analysis, we did additional two tests. First, we did an omnibus test of model coefficients versus a model with intercept only. This test detects whether a model is significant (P<0.05) or not; this is a test of the null hypothesis that adding any variables to the model has not significantly increased our ability to predict the dependent variable. A model is useless if the P-value in omnibus test was >0.05. Second, we did a Hosmer and Lemeshow goodness of fit test, which shows how well the model fits the data with P>0.05 indicating good fit; this is a test of the null hypothesis that there is a linear relationship between the predictor variables and the log odds of the criterion variable. The hit rate in multiple logistic regression analysis is a measure how well a model predicts the dependent variable.

Sub-analysis

In the sub-analysis, we also investigated what clinical and socio-demographic factors affected the five indicators of WCST in the multiple logistic regression analysis. We used multiple logistic regression analysis in the sub-analysis in order to compare the results between main and sub-analysis. In this analysis, the dependent variables were the five indicators of WCST and independent variables were the candidate clinical and socio-demographic factors. We compared the results of the multiple logistic regression analysis with the results of previous studies.[9 10 23]

Software

IBM SPSS statistical software (IBM Japan, Tokyo, Japan), version 19 was used for analyses. The significance level was set at P=0.05 using a two-tailed t-test.

RESULTS

Distribution of the WCST (CA, PEM, PEN, TE and DMS) scores in patients with schizophrenia is shown in Figure 1. The numbers of patients in the following analyses were CA n=131, PEM n=122, PEN n=131, TE n=115 and DMS n=131 because of missing values in the data.

Spearman's rank correlation coefficients between the five indicators of WCST are shown in Table 2. Although no strong correlation (>0.8) was observed in any of these clinical and socio-demographic factors, the Spearman's correlation between PANSS negative scale score and PANSS general psychopathology scale score was high (0.74).

Principal component analysis

Two factors (1 and 2) were identified in principal component analysis of the five indicators of WCST. Factor 1 mainly consisted of CA, PEM, PEN, and TE, and accounted for 65.6% of the total variance. Factor 2 mainly consisted of DMS and accounted for 23.2% of the total variance (Table 3 and Figure 2). We converted the factor 1 and factor 2 scores into categorical variables (1 or 0) using cutoff values. The cutoff values were the median values (factor 1: -0.299; factor 2: 0.080). We used these categorical variables as dependent variables in multiple logistic regression analysis.

Main analysis

Age, education years, and PANSS negative scale score significantly affected factor 1 score, and the duration of illness significantly affected factor 2 score in patients with schizophrenia (Table 4). The details of the results from the multiple logistic regression analyses are shown in Table S2 (Web only file). *P*-values in an omnibus test of model coefficients versus a model with intercept only were statistically significant ($P<0.05$) for all the models in WCST factor scores. In the Hosmer and Lemeshow goodness of fit test, all the models fit the data adequately with $P>0.05$. Factor 1 score may be predicted precisely by this model considering hit rate (0.77).

CPZ equivalent doses did not affect the WCST scores. PANSS positive scale score did not affect the WCST scores; whereas PANSS negative scale score did.

Sub-analysis

In the sub-analyses, age, education years, and PANSS negative scale score significantly affected CA score. Age and education years significantly affected PEM, PEN, and TE scores, and age significantly affected DMS score in patients with schizophrenia. The details of these results are shown in Table S3 and Table S4 (Web only file); Table S4 includes the results of previous studies. *P*-values in the omnibus test of model coefficients versus a model with intercept only were statistically significant ($P<0.05$) for all the models for each WCST score, and all the models fit the data adequately in the Hosmer and Lemeshow

goodness of fit test.

DISCUSSION

This study is the first to investigate the relationships between WCST factor scores and clinical and socio-demographic factors in Japanese patients with schizophrenia by multiple logistic regression analysis. We showed the distribution of each WCST score (Figure 1). We conducted principal component analysis and identified two factors. The components of these two factors were similar to previous studies.[19-21] Thus, we could reduce the number of WCST outcomes from five indicators to two factors (Table 3). In assessment of cognitive function in patients with schizophrenia, using the WCST factor scores may reduce the possibility of type I errors due to multiple comparisons. We analyzed the relationship between these two factors and clinical and socio-demographic factors with multiple logistic regression analysis. We found that age, education years, PANSS negative scale score, and duration of illness affected the two WCST factor scores.

Principal component analysis

Our study showed that factor 1 mainly consisted of CA, PEM, PEN, and TE and factor 2 mainly consisted of DMS. In the previous studies with principal component analysis and factor analysis of WCST scores in patients with schizophrenia, Categories Complete (CC) (an indicator examining numbers of categories achieved in the same way as CA), PE (an indicator examining perseveration in the same way as PEM and PEN) and TE mainly constituted one

factor. Failure to Maintain Set (FMS) (an indicator examining difficulty of maintaining set, similar to DMS) mainly constituted another factor.[19-21] Our results resembled the results of the principal component analysis and factor analysis of WCST in these previous studies.[19-21]

Factor 1, which included representative indicators (CC, PE, etc.), was named as 'general executive functioning' in a previous study.[21] Therefore, factor 1 in our study also may represent general executive functioning. In our study, factor 1 score showed a high contribution ratio of the total variance (65.6%) in principal component analysis of WCST scores in patients with schizophrenia. WCST factor scores calculated by principal component analysis may be useful for reducing the possibility of type I errors due to multiple comparisons. Factor 1 and factor 2 in our study resembled those in previous studies.[19-21] Therefore, the KWCST measures cognitive function similarly to the traditional WCST.

We compared the Spearman's rank correlation coefficients with the Pearson's product moment correlation coefficients between the five indicators of WCST (Table 2 and Table S1). Correlations between CA, PEM, PEN and TE and a correlation between CA and DMS were statistically significant (P<0.001). In this point, both correlation coefficients showed the same direction. Therefore, using Pearson's correlation matrix, instead of Spearman's correlation matrix, in principal component analysis may be justified in our study.

Main analysis

We identified clinical and socio-demographic factors (age, education

years, and PANSS negative scale score) affecting WCST factor 1 score. We also identified a clinical and socio-demographic factor (duration of illness) affecting WCST factor 2 score. This is an important new finding. Comparing the three main previous studies [9 10 23] with the current study, we summarized shared and different findings, shown in Table 4.

The shared findings were that age and PANSS negative scale score were related to WCST scores (Table 4).[9 10 23]

Two findings differed from previous studies (Table 4).[9 10 23] First, we found a new relationship between education years and WCST scores. Second, we found no relationship between age of onset and WCST scores. Differences in the results between previous studies [9 10 23] and our study may be explained by differences of ethnicity, distribution of age and education years, types of statistical analysis used, and the version of WCST. These differences suggest that future studies about WCST should be conducted with attention to these conditions.

CPZ equivalent doses did not affect the WCST scores in this study. This result was in the same direction as one meta-analysis (n=4524) though recent studies had suggested the possibility of an effect.[31 39 40] Future studies will be necessary to clarify whether CPZ equivalent doses affect WCST scores under other conditions.

PANSS positive scale score did not affect the WCST scores but the PANSS negative scale score did. A recent meta-analysis (n=6519) suggested that negative symptoms related to cognitive performance in patients with schizophrenia whereas positive symptoms did not.[41] This suggests that the

relationships between PANSS positive and negative scale scores and WCST scores in this study may be reasonable.

Sub-analysis

We found that factor 1 score and factor 1 score's main components (CA, PEM, PEN and TE) related to age and education years (Table S5 (Web only file)).

The effect of duration of illness on WCST factor 2 score, which was mainly influenced by DMS, is the novel finding of the main analysis. However, DMS is not significantly associated with the duration of illness in the sub-analysis (Table S5 (Web only file)). This discrepancy between the main analysis and sub-analysis may be derived from the difference between DMS and factor 2 (Factor 2 included not only DMS, but also CA, PEM, PEN and TE).

Limitations

There are several limitations in this study. First, other clinical and socio-demographic factors that were not investigated in the current study could affect WCST scores. Candidates for such clinical and socio-demographic factors are IQ,[42] participants' dominant arm, experience with using a computer, doses of drugs affecting cognitive performance (anticholinergics, benzodiazepines, etc), sleep,[43] eating, and risk factors of arteriosclerosis (BMI, blood pressure, etc).[44] It may be useful to include these factors in future studies. Second, the

WCST indicators (CA, PEM, PEN, TE and DMS scores) in our study did not cover all WCST indicators; we selected the major five indicators. We might find other factors by principal component analysis or new relationships between new WCST factors and clinical and socio-demographic factors if we included other clinical indicators. Third, instead of using Spearman's correlation matrix in the principal component analysis, which might be more appropriate method in terms of the non-normal distribution of five WCST indicators, we used Pearson's correlation matrix. Fourth, we dichotomized continuous variables (WCST factor scores) in the multiple logistic regression analysis. Therefore, careful interpretation of the results may be needed, considering the statistical weak points.[45]

Conclusion

This study is the first study that investigated clinical and socio-demographic factors affecting WCST factor scores calculated by principal component analysis in patients with schizophrenia. The study was conducted in a relatively large Japanese population. We showed distribution of measured five WCST indicators in patients with schizophrenia and confirmed two WCST factors by principal component analysis. Age, education years, PANSS negative scale score and duration of illness affected WCST scores in patients with schizophrenia. The interaction between the duration of illness and a factor of the WCST needs further confirmation in future studies because there was a discrepancy between the results of the main analysis and the sub-analysis in this study.

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FOOTNOTES

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Competing interests

None

Ethics approval

This study was approved under the guidelines for epidemiological studies by the Nagoya University Graduate School of Medicine and Nagoya University Hospital Ethics Review Committee and was conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from each subject before the start of the study.

Contributors

MB, TKo and NO conceived and designed the experiments. MB, TKo, TKi, KK and YA performed the experiments. MB, TKo, BA, TO, NK, TI and NO analyzed the data. MB, TKo and YA contributed reagents/materials/analysis tools. MB, TKo, TO, BA and NO wrote the paper.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

No additional data are available.

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FIGURE LEGENDS

Figure 1. Distribution of WCST scores in patients with schizophrenia (*n*=131)

None of the distribution was normal distribution.

Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set

[a]. Standard deviation

[b]. % of cases

Figure 2. Component plot in principal component analysis of WCST scores in patients with schizophrenia (*n*=131)

Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set

Table 1. Profiles of patients with schizophrenia

Table 2. Correlation coefficients for WCST scores in patients with schizophrenia

Table 3. Factor loadings in principal component analysis in patients with schizophrenia (*n*=131)

Table 4. Clinical and socio-demographic factors for WCST scores of patients with schizophrenia in the current study (main analysis) and for previous studies

APPENDICES

Table S1 (Web only file). Pearson's product moment correlation coefficients for WCST scores in patients with schizophrenia

Table S2 (Web only file). Multiple logistic regression analysis of WCST factor scores in patients with schizophrenia (*n*=131)

Table S3 (Web only file). Multiple logistic regression analysis of WCST scores in patients with schizophrenia (*n*=131)

Table S4 (Web only file). Clinical and socio-demographic factors for WCST scores of patients with schizophrenia in this study (sub-analysis) and previous studies

Table S5 (Web only file). Clinical and socio-demographic factors for WCST scores of patients with schizophrenia in this study (main analysis and sub-analysis)

Information S1 (Web only file). Why we did not use multiple linear regression analysis in this study.

Information S2 (Web only file). Why we used the median as a cutoff point for dependent variables (WCST factor scores) in the multiple logistic regression analysis.

Table 1. Profiles of patients with schizophrenia

		Patients with schizophrenia (n=131)	
Sex		Male	Female
		84	47
		Average	(SD[a])
Age (y)		43.5	(13.8)
Education (y)		12.4	(2.4)
Age of onset (y)		26.3	(10.0)
Duration of illness (y)		17.0	(12.8)
Chlorpromazine equivalent doses (mg)		618.4	(391.1)
PANSS scale	Positive (7-49)	16.5	(5.3)
	Negative (7-49)	19.3	(5.6)
	General (16-112)	36.6	(9.4)
	Total (30-210)	72.4	(18.1)

[a]. Standard deviation

Table 2. Correlation coefficients for WCST scores in patients with schizophrenia

		Patients with schizophrenia (n=131)				
		CA	PEM	PEN	TE	DMS
correlation coefficient[a]	CA	-	-	-	-	-
	PEM	-0.70**	-	-	-	-
	PEN	-0.79**	0.73**	-	-	-
	TE	-0.88**	0.71**	0.89**	-	-
	DMS	-0.58**	0.30*	0.28*	0.30*	-

*: P<0.01, **: P<0.001

Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set

[a]. Spearman's rank correlation coefficient

Table 3. Factor loadings in principal component analysis in patients with schizophrenia (*n*=131)

		factor 1	factor 2
WCST score	CA	-0.89	0.36
	PEM	0.84	0.27
	PEN	0.92	0.27
	TE	0.93	0.13
	DMS	0.29	-0.93
Variance (%) explained by each factor		65.6	23.2
Cumulative explained variance (%)		65.6	88.9

Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set

Factor analysis was based on principal component method without rotation.

Two factors were retained using the eigenvalue >1 criterion.

Table 4. Clinical and socio-demographic factors for WCST scores of patients with schizophrenia in the current study (main analysis) and for previous studies

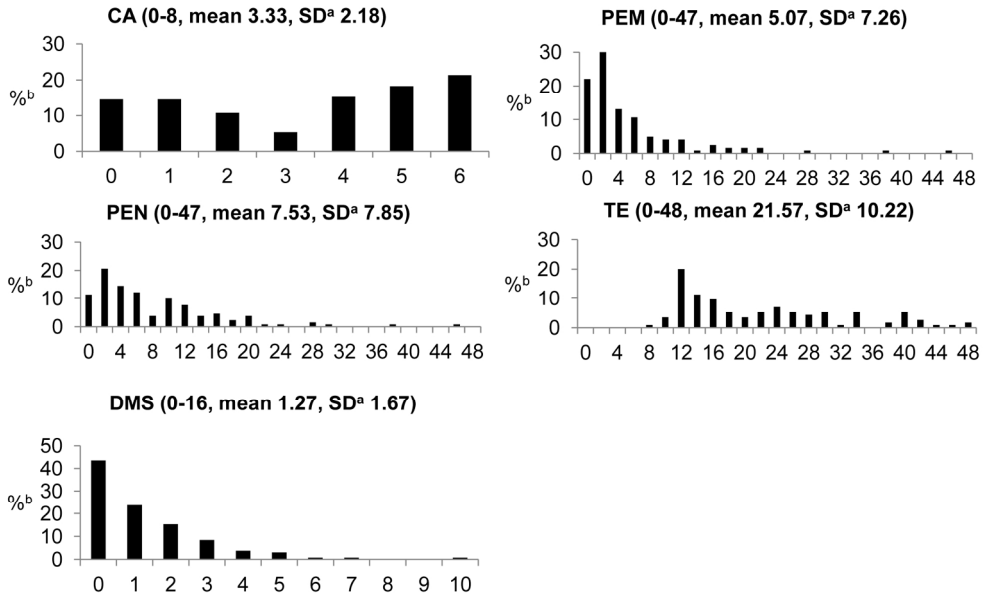
	Patients with schizophrenia (n=131) Main analysis		Previous studies		
	Factor 1 score	Factor 2 score	CA[a]	PE[a]	TE[a]
Sex			n/a	n/a	n/a
Age	***		n.s.[b]	○[b]	n/a
Education years	**		n.s.[b]	n.s.[b]	n/a
Age of onset			n.s.[c]	○[c]	n/a
Duration of illness		*	n.s.[b]	n.s.[b]	n/a
Chlorpromazine equivalent doses			n/a	n/a	n/a
PANSS score positive (7-49)			n.s.[d]	n/a	n/a
PANSS score negative (7-49)	*		○[d]	n/a	n/a
PANSS score general (16-112)			n.s.[d]	n/a	n/a
hit rate	0.77	0.58	n/a	n/a	n/a

*: P<0.05, **: P<0.01, ***: P<0.001

Abbreviations: CA, Categories Achieved; PE, Perseverative errors; TE, Total Errors; n/a, data not available; n.s., not significant

[a]. CA, PE and TE were included in factor 1 in a previous study.

[b]. Reference 10, [c]. Reference 23, [d]. Reference 9



None of the distribution was normal distribution.
Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set
[a]. Standard deviation
[b]. % of cases

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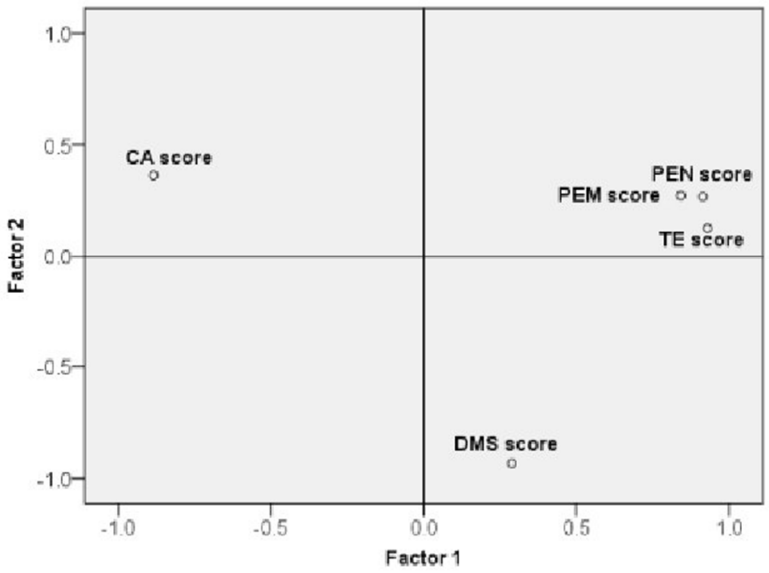

Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set

Table S1. Pearson's product moment correlation coefficients for WCST scores in patients with schizophrenia

		Patients with schizophrenia (*n* =131)				
		CA	PEM	PEN	TE	DMS
correlation coefficient[a]	CA	-	-	-	-	-
	PEM	-0.57**	-	-	-	-
	PEN	-0.68**	0.82**	-	-	-
	TE	-0.82**	0.70**	0.85**	-	-
	DMS	-0.53**	0.06	0.04	0.11	-

**: *P*<0.001

Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set

[a]. Pearson's product moment correlation coefficient

Table S2. Multiple logistic regression analysis of WCST factor scores in patients with schizophrenia (*n*=131)

Forward-backward stepwise selection, Setting: P_{in}=0.05, P_{out}=0.1								
		Factor 1 score				Factor 2 score			
		B[a]	Exp(B)[b]	95% CI[c]	*P*-value	B[a]	Exp(B)[b]	95% CI[c]	*P*-value
Sex (Male 1, Female 0)		-	-	-	-	-	-	-	-
Age (y)		0.06	1.06	1.03-1.10	**<0.001**	-	-	-	-
Education (y)		-0.39	0.68	0.54-0.85	**0.001**	-	-	-	-
Age of onset (y)		-	-	-	-	-	-	-	-
Duration of illness (y)		-	-	-	-	-0.03	0.97	0.94-1.00	**0.03**
CPZeq (mg/day)		-	-	-	-	-	-	-	-
PANSS score	Positive (7-49)	-	-	-	-	-	-	-	-
	Negative (7-49)	0.11	1.12	1.02-1.22	**0.01**	-	-	-	-
	General (16-112)	-	-	-	-	-	-	-	-
Intercept		-0.03	0.97	-	0.98	0.55	1.73	-	0.08
omnibus test		***P*<0.001**				**0.02**			
Hosmer and Lemeshow test		0.12				0.85			
hit rate		0.77				0.58			

Abbreviations: CPZeq, Chlorpromazine equivalent doses

[a]. Regression coefficient

[b]. This is the exponentiation of the B coefficient, which is an odds ratio.

[c]. Confidence interval of Exp(B)

Cutoff values were factor 1: -0.299, factor 2: 0.080.

0 and 1 are dummy variables in respect to subjects' sex.

Considering omnibus test *P*-values, these models are significant (*P*<0.05).

Considering Hosmer and Lemeshow test *P*-values (*P*>0.05), factor 1 score and factor 2 score may be predicted by this model.

Table S3. Multiple logistic regression analysis of WCST scores in patients with schizophrenia (*n*=131)

Forward-backward stepwise selection, Setting: P_{in}=0.05, P_{out}=0.1																				
		CA				PEM				PEN				TE				DMS			
		B[a]	Exp(B)[b]	95% CI[c]	*P* -value	B[a]	Exp(B)[b]	95% CI[c]	*P* -value	B[a]	Exp(B)[b]	95% CI[c]	*P* -value	B[a]	Exp(B)[b]	95% CI[c]	*P* -value	B[a]	Exp(B)[b]	95% CI[c]	*P* -value
Sex (Male 1, Female 0)		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Age (y)		-0.06	0.94	0.92-0.97	**<0.001**	0.03	1.03	1.00-1.06	**0.04**	0.05	1.05	1.02-1.08	**0.001**	0.06	1.06	1.03-1.10	**<0.001**	0.03	1.03	1.01-1.06	**0.02**
Education (y)		0.31	1.36	1.13-1.64	**0.001**	-0.33	0.72	0.59-0.87	**0.001**	-0.19	0.83	0.70-0.97	**0.02**	-0.35	0.70	0.57-0.87	**0.001**	-	-	-	-
Age of onset (y)		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Duration of illness (y)		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CPZeq (mg/day)		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PANSS score	Positive (7-49)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Negative (7-49)	-0.08	0.92	0.85-0.99	**0.03**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	General (16-112)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Intercept		0.52	1.68	-	0.72	3.21	24.70	-	**0.02**	0.37	1.45	-	0.76	1.76	5.79	-	0.22	-1.12	0.33	-	0.07
omnibus test		***P* <0.001**				***P* <0.001**				***P* <0.001**				***P* <0.001**				**0.02**			
Hosmer and Lemeshow test		0.44				0.76				0.56				0.56				0.88			
hit rate		0.69				0.66				0.62				0.71				0.60			

Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set; CPZeq, Chlorpromazine equivalent doses

[a]. Regression coefficient

[b]. This is the exponentiation of the B coefficient, which is an odds ratio.

[c]. Confidence interval of Exp(B)

Cutoff values were CA: 4, PEM: 2, PEN: 5, TE: 18, DMS: 1.

0 and 1 are dummy variables in respect to subjects' sex.

Considering omnibus test *P*-values, these models are significant (*P*<0.05).

Considering Hosmer and Lemeshow test *P*-values (0.05<*P*), CA, PEN, PEM, TE and DMS scores may be predicted by this model.

Table S4. Clinical and socio-demographic factors for WCST scores of patients with schizophrenia in this study (sub-analysis) and previous studies

	Patients with schizophrenia (*n* =131) Sub-analysis					Previous studies		
	CA	PEM	PEN	TE	DMS	CA	PE	TE
Sex						n/a	n/a	n/a
Age	***	*	**	***	*	n.s.[b]	◯[b]	n/a
Education years	**	**	*	**		n.s.[b]	n.s.[b]	n/a
Age of onset						n.s.[c]	◯[c]	n/a
Duration of illness						n.s.[b]	n.s.[b]	n/a
Chlorpromazine equivalent doses						n/a	n/a	n/a
PANSS score positive (7-49)						n.s.[d]	n/a	n/a
PANSS score negative (7-49)	*					◯[d]	n/a	n/a
PANSS score general (16-112)						n.s.[d]	n/a	n/a
hit rate	0.69	0.66	0.62	0.71	0.60	n/a	n/a	n/a

*: *P*<0.05, **: *P*<0.01, ***: *P*<0.001

Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set; PE, Perseverative errors; n/a, data not available; n.s., not significant

[a]. Reference 10

[b]. Reference 23

[c]. Reference 9

Table S5. Clinical and socio-demographic factors for WCST scores of patients with schizophrenia in this study (main analysis and sub-analysis)

	Patients with schizophrenia (*n* =131)						
	Main analysis		Sub-analysis				
	Factor 1 score	Factor 2 score	CA[a]	PEM[a]	PEN[a]	TE[a]	DMS[b]
Sex							
Age	***		***	*	**	***	*
Education years	**		**	**	*	**	
Age of onset							
Duration of illness		*					
Chlorpromazine equivalent doses							
PANSS score positive (7-49)							
PANSS score negative (7-49)	*		*				
PANSS score general (16-112)							
hit rate	0.77	0.58	0.69	0.66	0.62	0.71	0.60

*: *P*<0.05, **: *P*<0.01, ***: *P*<0.001

Abbreviations: CA, Categories Achieved; PEM, Perseverative Errors in Milner; PEN, Perseverative Errors in Nelson; TE, Total Errors; DMS, Difficulties of Maintaining Set

[a]. CA, PEM, PEN and TE were included in factor 1 in this study.

[b]. DMS was included in factor 2 in this study.

Information S1. Why we did not use multiple linear regression analysis in this study.

We chose multiple logistic regression because of the distribution of the dependent variables (WCST factor scores). To conduct multiple linear regression analysis, normality of dependent variables is needed.[1] The distribution of the dependent variables (WCST factor scores) in this study was not normal because the *P*-values of two kinds of normality tests (Kolmogorov-Smirnov test and Shapiro-Wilk test) were less than 0.001. We also tested normality of the logarithmic distribution of the dependent variables (WCST factor scores); the *P*-values on both types of normality test (Kolmogorov-Smirnov test and Shapiro-Wilk test) were less than 0.001. Therefore, we used multiple logistic regression which can analyze variables in non-normality.[2]

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1. Osborne JW, Waters E. Four Assumptions Of Multiple Regression That Researchers Should Always Test. Practical Assessment, Research, and Evaluation 2002;**8**:1-9.

2. Peng CYJ, Lee KL, Ingersoll GM. An introduction to logistic regression analysis and reporting. J Educ Res 2002;**96**:3-14.

Information S2. Why we used the median as a cutoff point for dependent variables (WCST factor scores) in the multiple logistic regression analysis.

There were two reasons that we used the median as a cutoff point for the dependent variables (WCST factor scores) in our multiple logistic regression analysis. First, a previous psychiatric research report used the median as a cutoff point in dependent variables for multiple logistic regression analysis.[1] Second, the most common approach for dichotomizing continuous variables was to take the sample median because there were no cutoff points of WCST factor scores in previous studies.[2]

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1. Jackson CT, Fein D, Essock SM, Mueser KT. The effects of cognitive impairment and substance abuse on psychiatric hospitalizations. Community Ment Health J 2001;**37**:303-12.

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